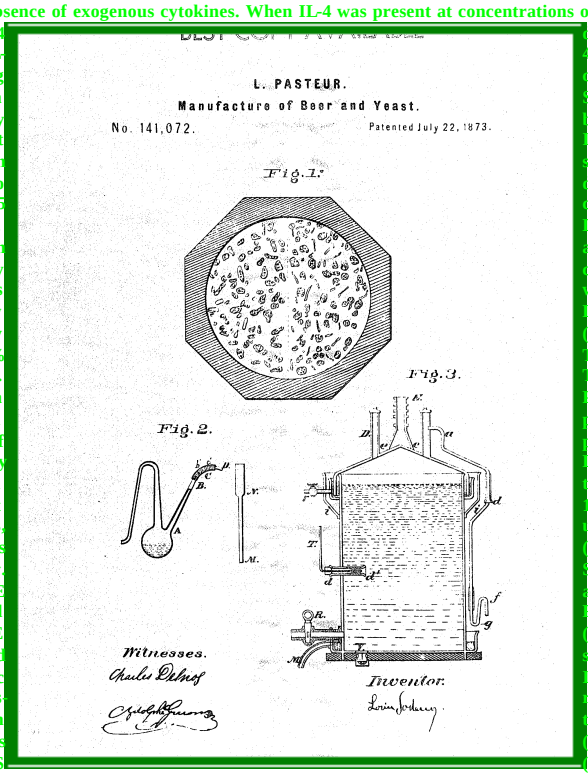
Intellectual Property and Biotechnology:

A Training Handbook



A training resource for developing countries in the APEC region funded under the APEC Support Program of the Australian Agency for International Development (AusAID)

December 2001

FOREIGN AFFAIRS AND TRADE

AUSTRALIA

AusAID the Australian Government's overseas aid program

Acknowledgements

This handbook was partly funded by the Australian Agency for International Development (AusAID) under the APEC Support Program, within a project administered by the Australian Department of Foreign Affairs and Trade (DFAT). It aims to supplement and promote the valuable cooperation undertaken by the APEC Intellectual Property Rights Experts' Group.

IP Australia and the Plant Breeders' Rights Office provided considerable support and guidance in the course of this program, and their assistance is warmly appreciated. This handbook does not embody or endorse any formal policy position on the part of any of its contributors, and does not represent the official views of the Australian Government or any of its agencies.

This handbook builds on training programs conducted in Melbourne, Hanoi, Bangkok, Beijing, Jakarta, Padang and Solo from 1998 to 2001. We acknowledge with warm gratitude the valuable support, input and involvement of the following people who made various contributions to the conduct of the training programs or in the preparation of this handbook. Any errors and omissions in this handbook are, however, wholly the responsibility of the editors.

Ms Dianne Angus, Florigene Ltd
Dr Ian Barr, CSL Limited
Ms Paula de Bruyn, Davies Collison Cave
Dr Andrew Christie, University of Melbourne
Dr Ian Cooke,Macfarlane Burnet Centre
Ms Catherine Hawkins
Ms Sandra Henderson, DFAT
Mr Dave Herald, IP Australia
Mr Adam Liberman, Freehills
Ms Cheryl McCaffery, eclIPse IP Management
Dr Carol Nottenburg, CAMBIA
Dr Tania Obranovich, Davies Collison Cave
Mr Leo O'Keeffe, IP Australia
Dr William Pickering, FB Rice and Co
Ms Maree Ringland, DFAT
Dr Thomas Quirk, Biota Holdings Ltd
Mr Malcolm Royal, Phillips Ormonde and Fitzpatrick
Mr Desmond Ryan, Davies Collison Cave
Dr Vivien Santer, Griffith Hack
Mr John Slattery, Davies Collison Cave
Mr John Stonier, Davies Collison Cave
Mr Antony Taubman, Australian National University
Dr Cassandra Thumwood, Ludwig Institute
Dr Lyndal Thorburn, Advance Consulting
Professor Geoffrey Tregear, Howard Florey Institute
Mr Leigh Tristram, IP Australia
Mr Doug Waterhouse, Plant Breeders' Rights Australia

The many participants in these programs have also provided invaluable input, and this is acknowledged with gratitude. We thank AMRAD for its support for the training program. We also thank *New Scientist*, Dr. Niall, and *Signals* for their permission to reproduce extracts from their publications in *Module Six* and *Module Nine*, *Nine*, and Monsanto Australia for the use of the INGARD Technology User Agreement in *Module Ten.*
The principal author of this publication is Antony Taubman.

PLEASE NOTE

This handbook is designed to provide a practical introduction to the nature and management of intellectual property rights in relation to biotechnology. It is intended to contribute material for use in training courses, to assist in raising awareness of some of the complex issues that surround the protection and management of intellectual property in the field of biotechnology, and to assist in the development of practical skills.

The handbook does not seek to provide legal, managerial or technical advice on intellectual property law. It should in no way be considered a substitute for expert legal, technical and managerial advice. You should seek qualified professional advice on any aspect of intellectual property law and management, and should not rely on this handbook.

This handbook does not expressly represent the official view of the Australian Government or any of its agencies, and is not intended to sanction or advocate any particular policy position or viewpoint.

We have endeavoured to ensure that the contents of this handbook are accurate and correct, but there may be errors or omissions. Kindly advise of any errors, inaccuracies or significant omissions to the address below so they can be rectified in later versions.

Comments and suggestions as to how the handbook could be usefully enhanced or extended would also be gratefully received.

An on-line version of this handbook, with any updates and amendments, will be available at http://www.dfat.gov.au/ip

Enquires concerning the Handbook can be directed to:
The Director, International Intellectual Property Section
Office of Trade Negotiations
Department of Foreign Affairs and Trade
Barton ACT 0221 Australia
Tel: + 61 2 6261 2039 Fax: + 61 2 6261 3514
ip@dfat.gov.au

[intentionally blank]

TABLE OF CONTENTS

[intentionally blank]

How to use this handbook

Who is this handbook for?

This handbook does not assume any background in intellectual property law or in biotechnology. It is aimed at a general audience, including scientific researchers, public research institutions, commercial research institutions, businesspeople, industry associations, academics, lawyers, policy makers, officials in government intellectual property offices and individuals with an interest in biotechnology and intellectual property. Part Two, on managing intellectual property, is written mostly from the perspective of researchers in public sector institutions and universities, but should be of interest to other groups as well.

What is the aim of the handbook?

The handbook does not attempt to provide advanced technical training in the complex field of intellectual property and biotechnology. It does aim at giving an overview of the key concepts and the legal framework, and a practical understanding of how they are applied in practice. It is therefore intended to provide basic tools for using the IP system and to lay the groundwork for further study and research.

Using the handbook

This handbook is designed with ten self-contained modules. It can be used:

- for an intensive specialist training course, which covers all the modules at once; or
- for specific training on one particular topic (e.g. using patent information or plant breeder's rights), when you can pick and choose which modules to do accordingly.

The modular structure of the handbook is intended to ensure it can be used flexibility. This means there is some overlap in subject matter between modules, but this has been found helpful in consolidating understanding when undertaking longer training courses.

The handbook can be used for individual or group training. It was created and tested as a resource for group training activities ranging from two days to two weeks. The exercises are therefore written with the needs of a group in mind, particularly the major exercises on patent law in *Module Five* and *Module Six*. To be run as planned, the major group exercises will need some advance organisation (including the availability of facilitators if possible), and preparation of the individual bundles of documents for each distinct group. Individual users of the handbook can work through the group exercises considering the perspective of each separate interest group represented in each case.

Each module follows the same format. The objectives for each module are set out at the beginning so that you know which are the most important points for you to focus on. Most modules include examples to help you understand the issues discussed. Each module also concludes with a summary. Each modules has a set of group exercises. These are not intended for assessment purposes, but rather to stimulate group discussion about the issues raised, and to give some practical experience in applying the information and skills covered in the module. Individual users of the handbook can also use these exercises to check whether they have understood the material covered in the module before moving on.

Overview

Introduction

Biotechnology in one form or another has been part of human development since the dawn of agriculture. Human ingenuity has led to increased production and greater diversity and quality of livestock and varieties of crops. Today's food crops and domestic animals embody the benefits of many generations of selection and breeding.

Biotechnology continues to offer considerable potential for enhancing human health and well-being. Modern biotechnology, including gene technology, is finding increasing application in healthcare and in a host of industrial and agricultural industries. Effectively applied, modern biotechnology may contribute to economic growth, technological development and human welfare. Yet it has also raised concerns about ethical and moral issues, equitable sharing of the benefits of biotechnology, environmental impact, the accelerated pace of change and the regulatory challenges. Intellectual property (IP) rights are not new in the biotechnology domain, but some of the concerns about modern biotechnology have focussed on the nature, impact and legitimacy of IP rights as they are applied to gene technology and to inventions that draw on genetic resources and associated traditional knowledge.

Just as the impact of modern biotechnology is beginning to be felt, there is increasing recognition of the importance of a balanced IP system in assuring economic development. Many countries are currently building IP issues into their economic, industrial and technological planning, and into research and education programs. This leads to a debate about balancing public and private interests - on the one hand, providing sufficient incentives for the investments required to bring new technologies to the public, and on the other ensuring that there is sufficient flexibility and capacity for ensuring that the benefits of new technologies are widely available on equitable terms. In relation to biotechnology, there are also concerns that IP rights do not encompass material in the public domain or that has been somehow misappropriated. The important debate on how best to achieve this balance is continuing at national and international levels: this handbook does not seek to advance any particular point in this policy discussion, and focusses instead on describing the current system with reference to general international standards.

There is no doubt that reaping the social benefits and potential value of IP, however the overall balance of interests is struck, does require a practical understanding of how the IP system operates and how IP rights can be used and managed most effectively. This handbook concentrates on this area of awareness and expertise, in the hope that it will assist in the more effective use of the IP system to achieve the positive outcomes that are hoped for. It aims to encourage a view of the IP system as more than an inert collection of legal documents, so that it becomes a toolkit for development of and access to technologies, and a means of ensuring their beneficial application. Not all researchers need to become patent experts, but many are under pressure to make better use of the IP system to assist in ensuring that their research outcomes can be effectively disseminated and used, and often to ensure improved funding for future research programs. This handbook is intended to make a modest contribution to fulfilling these needs.

The scope of the handbook

The handbook aims to cover the following general topics:

- the range and different types of IP rights,
- the international framework for the protection of IP,
- how patent law protects biotechnology inventions,
- the legal requirements and administrative steps for getting a patent,
- how databases of technical and patent information can help in research,
- how to search databases for technical and patent information,
- how to read, interpret and assess the effect of a patent document,
- the nature of plant breeder's rights systems,
- IP as a factor in a research and development,
- how to negotiate research contracts with commercial partners, and
- the management and practical use of IP rights, including licensing and enforcement.

STRUCTURE AND CONTENTS

Part One of the handbook – 'Intellectual Property Law' - focusses on the principles and key features of intellectual property (IP) law, with particular reference to biotechnology IP. It provides an introduction to patents and the use of patent documentation as source of technological information, and has two extended group exercises which allow for in depth application and discussion of the principles of patent law. It also covers separate systems for plant variety protection. Part Two – 'Using Intellectual Property' - then looks at how IP rights are used in practice to achieve benefits such as commercialisation of research, access to technology and the dissemination to the public of new technologies. It concludes with case studies on the use of IP rights in bringing new technologies to the market.

Module One: Introduction to Intellectual Property

This provides an overview of the chief forms of IP rights potentially relevant to biotechnology – patents, plant breeders rights, confidential information (or trade secrets), trade marks and geographical indications. It covers some of the key international agreements on IP and some of the principles they give effect to. It also briefly reviews some of the reasons put forward for protecting IP, and some criticisms of the IP system.

Module Two: Biotechnology and Intellectual Property

This module goes into more detail about IP as it applies to biotechnology, with a particular concentration on patents and the principles of patent law – looking particularly at the nature of a patent right, and the tests an invention must pass to be eligible for a patent. The module's exercises include looking at two patents that have been the subject of much international debate, one concerning turmeric and one on rice.

Module Three: Reading a Biotechnology Patent and the Patent Process

This module considers the details of the patent system, looking at the contents of patent documents, the interpretation of patent claims, and the processes that lead to a patent, including the international system known as the PCT (Patent Cooperation Treaty).

Module Four: Searching Patent Databases

This module considers one of the key practical uses of the patent system, its role as a source of technological information and information on rights that may affect research and development programs. It covers the practical skills that are needed to access patent information, and how it can be used to avoid 'reinventing the wheel,' to monitor emerging technologies, and to avoid conflict with existing rights.

Module Five: Group Exercise on Patent Validity: Neem

This exercise gives practical exposure to preparing, analysing and opposing a patent application in a relatively simple field of technology (although one that raises strong concerns about the use of genetic resources and traditional knowledge), and considering legal criteria such as novelty and inventiveness, as well as exclusions on patentability. Ideally, it should be run with participants organised in four groups, each group playing a particular role in relation to the patent.

Module Six: Group Exercise on Patent Validity: Relaxin

This exercise looks in more detail at key legal principles such as inventiveness and exclusions from patent rights on moral grounds, and applies them to a more complex biotechnology patent involving DNA sequences. This exercise is also organised to be run with four groups. Because of the complexity of the technology, it is preferable to use facilitators and to circulate the relevant documents well in advance of the exercise.

Module Seven: Plant Breeders' Rights

This module describes the separate system of protection for plant varieties, often termed plant breeders' rights. It contrasts these rights with the patent system, and sets out the international framework for plant variety protection.

Module Eight: Researching and Intellectual Property Rights

This module considers the practical needs of a researcher and considers the various ways the IP system affects research and development – such as research agreements, confidentiality agreements, laboratory notebooks, and the negotiation of freedom to operate in relation to other IP rights.

Module Nine: Licensing and Enforcing Intellectual Property Rights

This module considers what happens after research has been successfully concluded, and it comes to put the product on the market. What options are there for licensing IP and otherwise commercialising or disseminating research, and how are IP rights enforced? The module considers the issues raised in license negotiation, such as ownership and validity of IP rights, royalty rates, territory, exclusivity, allocation of costs and responsibilities for maintaining and enforcing IP rights, confidentiality and publication issues, insurance, release and indemnity and dispute resolution and termination.

Module Ten: Case Studies on Commercialising Research

This module discusses general issues arising from the increasing pressure on research institutes to commercialise their work. It then considers an hypothetical case of negotiations on freedom to operate in relation to existing IP rights, and describes the path to commercialisation in Australia of Bt cotton, the first transgenic crop approved for commercial release.

FOREIGN AFFAIRS AND TRADE

AUSTRALIA

AusAID the Australian Government's overseas aid program

Module One

Introduction to Intellectual Property Law

Intellectual Property and Biotechnology:
A Training Handbook

Contents: Module One

1.1 Objectives for Module One

This Module provides an introduction to:

- the different types of intellectual property rights relevant to biotechnology including patents, plant breeders' rights, trade secrets, trade marks and geographical indications.
- various rationales for the intellectual property system
- the international intellectual property treaties relevant to biotechnology including:
  - the World Trade Organisation (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS)
  - the Paris Convention for the Protection of Industrial Property
  - the Patent Cooperation Treaty (PCT)
  - the Budapest Treaty for the Deposit of Microorganisms
  - the Strasbourg Agreement Concerning the International Patent Classification
  - the International Convention for the Protection of New Varieties of Plants (UPOV)
- other international agreements relevant to biotechnology including:
  - the Convention on Biological Diversity (CBD), and
  - the Food and Agriculture Organisation (FAO) Treaty on Access to Plant Genetic Resources for Food and Agriculture.

1.2 What is Intellectual Property?

Intellectual property is a cluster of legally recognized rights associated with innovation and creativity – the works of the mind, as against physical products, land and other tangible resources. Even though it is intangible, intellectual property (IP) is often recognized as personal property, to be sold and traded like other forms of property. But national laws normally don't define 'intellectual property' as a single property right. Instead, 'intellectual property' is used as a convenient general term describing a range of distinct legal rights. Within this spectrum, intellectual property rights can be very different from one another, in their subject matter, in the way they are defined, administered and enforced, and in the way they impact on other people. The general concept of 'intellectual property' is usually taken to cover specific rights relating to:

- patents
- trade marks
- trade secrets (or undisclosed information)
- copyright and rights related to copyright (such as rights of performers, producers and broadcasters)
- plant breeders' rights
- industrial designs
- integrated circuit designs
- geographical indications

'Industrial property' is a term used specifically for patents, designs and trade marks, in contrast to copyright and the related rights of performers, broadcasters and producers. You might also see the terms *intellectual capital* and *knowledge capital*. These terms are generally used to describe the intangible, but often highly valuable, assets of business enterprises that are embodied in the know-how, skills and specific knowledge of their personnel. This may include the material technically recognised as intellectual property (such as the patents and trade marks owned by a company). It also includes the background knowledge and capacities that make for a successful enterprise, which is not clearly defined or subject to specific legal protection. Intellectual capital can be very roughly measured by the difference between the market's valuation of a company (the value of all its stock on the stock exchange), and the value of its tangible assets - cash, other financial assets, physical property, goodwill, equipment and the like. Unlike 'intellectual property,' intellectual capital is not a specific legal term, although in some writings, the two terms are used in place of each other.

'Intellectual capital' and 'knowledge capital' can also refer to a society's or a community's collective intellectual resources, including its research capacity, its technological skills and its traditional knowledge. In recent years, increasing attention has been paid to the role of intellectual property and intellectual capital in economic and social development, but the idea is not new, as is illustrated by the following quote, from *The National System of Political Economy*, written by the German economist Friedrich List in 1841:

> The present state of the nations is the result of the accumulation of all discoveries, inventions, improvements, perfections and exertions of all generations which have lived before us: they form the intellectual capital of the present human race, and every separate nation is productive only in the proportion in which its has known how to appropriate those attainments of former generations and to increase them by its own acquirements.

The value of intellectual capital can be extremely high, both for a society and for individual companies. Increasingly, the largest companies are defined by high levels of intellectual capital, both in the form of specific intellectual property rights and as informal kinds of know-how and knowledge.

One estimate of the intellectual capital in the world's most valued companies in 1997 is as follows:

Company	**GE**	**Shell**	**Microsoft**	**Exxon**	**Coca-Cola**	**Intel**	**Nippon**	**Merck**	**Toyota**	**Novartis**
Market value ($bn)	222	191	160	158	151	151	146	121	117	104
Equity ($bn)	34	77	11	44	7	19	43	13	46	22
Intellectual capital ($bn)	**188**	**114**	**149**	**114**	**144**	**132**	**103**	**108**	**71**	**82**

Some formal definitions

The terms *intellectual property* and *industrial property* can often be used in a very general sense, but they do have specific legal meanings. Perhaps the most important definitions are given in the key international treaties on the subject.

The World Intellectual Property Organization (WIPO) is the United Nations specialized agency responsible for international cooperation on IP. *The Convention establishing WIPO* defines the scope of this cooperation in general terms, beyond the precise legal rights defined in national laws. The Convention defines *intellectual property* as including the rights relating to:

- literary, artistic and scientific works;
- performances of performing artists, phonograms, and broadcasts;
- inventions in all fields of human endeavor;
- scientific discoveries;
- industrial designs;
- trademarks, service marks, and commercial names and designations;
- protection against unfair competition; and
- all other rights resulting from intellectual activity in the industrial, scientific, literary or artistic fields.

For the purposes of the World Trade Organization (WTO) *Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS)*, "intellectual property" is given a more limited application. It refers only to those categories of IP right that are explicitly covered in the Agreement's provisions on copyright and related rights, trademarks, geographical indications, industrial designs, patents, layout-designs (topographies) of integrated circuits and protection of undisclosed information. A copy of TRIPS is provided at *Annex One*.

The Paris Convention for the Protection of Industrial Property defines its subject matter in general terms:

> The protection of industrial property has as its object patents, utility models, industrial designs, trademarks, service marks, trade names, indications of source or appellations of origin, and the repression of unfair competition. Industrial property shall be understood in the broadest sense and shall apply not only to industry and commerce proper, but likewise to agricultural and extractive industries and to all manufactured or natural products, for example, wines, grain, tobacco leaf, fruit, cattle, minerals, mineral waters, beer, flowers, and flour.

Intellectual property rights (IPRs) are designed to protect the products of creative and inventive endeavours, and distinctive marks for traded goods and services. The grant of an IPR generally involves a trade-off, and some form of reciprocal obligation on the part of the right holder. For example, as a condition of receiving and maintaining a patent, inventors are required to make public details of their invention and may be required to ensure that the benefits of the invention are made available to the public on reasonable terms. Intellectual property rights form part of a nation's policy to encourage innovation and dissemination of knowledge, and are therefore intended to balance the interests of the inventor or originator with the broader needs of society.

This policy consideration is recognised in, and underscores, the TRIPS Agreement:

> The protection and enforcement of intellectual property rights should contribute to the promotion of technological innovation and to the transfer and dissemination of technology, to the mutual advantage of producers and users of technological knowledge and in a manner conducive to social and economic welfare, and to a balance of rights and obligations.

While different types of IPRs, such as patents and copyright, developed separately, they all set out to achieve this same objective of a balance of interests that promotes general welfare.

Some general principles

The move towards international cooperation on IP originated in the limited recognition of foreign claimants' interests in national IP systems. It was often difficult or impossible for foreigners to gain effective intellectual property rights in many countries. The problems this caused, and the difficulties in trade relations between countries, were obvious as early as the 19th Century.

This led to general recognition of the principle of 'national treatment.' A country that applies the principle of national treatment agrees to extend to foreigners at least the same entitlements and benefits it provides to its own nationals. For instance, this means that a foreign patent applicant receives at least the same treatment as nationals in the patent application and examination processes, and pays the same fees to the patent office. National treatment in intellectual property is recognised in international treaties – including the first major multilateral agreements on IP, the Paris Convention (on industrial property) of 1883, and the Berne Convention (on copyright) of 1886.

TRIPS is today an important international treaty on IP, providing a framework for an harmonised international system of IP rights, building on the framework created especially by the Paris and Berne Conventions and a number of other agreements. TRIPS applies the principle of national treatment over a wide range of IPRs, which ensures equitable access to the IP systems of other countries. This means, for example, that an Indonesian national who has developed an invention or created an artistic work enjoys rights and privileges in most other countries at the same level of nationals of those countries.

TRIPS also provides for detailed standards on the substance of IP law. For instance, it specifies that computer software should be protected by copyright, and that patent rights should be available for a period of at least twenty years. It also specifies principles that should apply to administering and enforcing IPRs, and makes use of the WTO's dispute settlement system to resolve disputes. Because most people using this training material will be working in countries where the TRIPS standards either apply already or are being put into place, this material refers to the standards set out in TRIPS when discussing IP rights.

PATENTS

Patents are limited rights based on a claim that a new technological invention has been created and fully communicated to the public. Essentially they put a fence around territory which is claimed to be an entirely new contribution to human technological knowledge. It is a fundamental principle of patent law that no patent should give rights to prevent people from using existing knowledge or technology that is already available to the public at the date of the patent. In other words, the fence should not be put around terrain which is already public domain, or which belongs to someone else. It should only cover terrain that is genuinely new, and indeed would not have existed without a significant inventive contribution by the inventor. Governments can require,

as a condition of granting the patent right, that other interested parties should have reasonable access to this terrain – so the fence is not an absolute barrier, and others can enter the patented terrain for research, education, and other public interest needs. Governments can also compel the patent owner to give others access to this territory – a 'compulsory licence' which, in effect, requires sections of the fence to be lowered – in certain cases when the public benefits of the new invention have been unduly restricted

Patents rights are only available as the result of a positive decision to grant a patent, and this is usually preceded by some form of examination and check that the claims for patent protection are valid and legitimate.

What is protected by patent law?

Patents do not cover abstract ideas or theories, but are intended to cover specific technical solutions that have some practical application, use or benefit. A patent is generally available for an eligible *invention*. Quite what constitutes an 'invention' for the purposes of getting a patent is a matter of some debate and legal uncertainty, and there are differences between the legal approaches taken in different countries.

Patents can cover new products (such as a new polymer or a new ceramic material), processes that create these new products (such as the method required to create the new polymer), new processes for producing existing products (such as a more efficient way of producing glass), and new processes generally (such as a new method for applying fertilizer to a crop). Often a single patent can cover several different products and processes as well - provided they are expressions of the same basic inventive concept.

For example, one patent which has been widely debated, US patent 5,663,484 entitled *Basmati rice lines and grains*, included claims for:

- a rice plant with certain defined characteristics, defined in several different ways
- a seed produced by this rice plant
- a rice grain derived from that seed.
- a progeny plant of the claimed rice plant
- a rice grain with characteristics corresponding to the claimed plant
- three related methods for selecting a rice plant for breeding or propagation

In all, in this patent, the claimed invention was covered by 20 inter-related claims, some containing more detailed versions of broader claims. The patent document describes in some detail how all of this disparate claimed material is linked to the same underlying inventive concept, relating to a breeding process guided by associating the 'starch index' with desirable qualities of rice. It also describes the background to this claimed invention, and gives details of the research and breeding processes that led to it. This patent is considered further in the case study at the end of *Module Two: Intellectual Property and Biotechnology*.

EXAMPLE OF AN INVENTION – CONCEPTION AND REDUCTION TO PRACTICE

Ideas are easy to come by but reduction to practice is an arduous but inspirationally rewarding matter
- Buckminster Fuller.

Say you are a biotechnology researcher, and you have come up with an idea for a new way of using a certain class of bacteria to treat organic waste. Based on its general properties and after some speculation on your part, you suspect that in the right conditions at least some of these bacteria could process waste into a stable by-product that would be a useful fertilizer. So far, you're not sure whether this idea will work in practice or how to put it into effect on a large scale. You might also need to work out which particular bacterium within the general class is going to achieve the desired outcome – and you may even need to modify the bacteria to make them more effective. Your original idea may be valuable, and potentially a major benefit both for the environment and for agriculture. But it probably wouldn't be eligible for a patent, because a patented invention has to be a tangible outcome, not scientific speculation or an exercise of the imagination.

Patents generally require that the invention as claimed be useful or functional, and a description of how it can be put into practice. A famous US Supreme Court decision stated that:

... a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.

Patent law in most countries requires an invention to be something that has a clear practical outcome. For example, US patent law distinguishes two stages in developing an invention that can be protected by a patent - the *conception* of the invention, and its *reduction to practice*. Once your research has proceeded to the point where you are reasonably confident that the idea can be put into practice, and you have developed a way of putting it to work, then it might be eligible for a patent. In this case, you might be able to obtain a patent for the resulting method for treating organic waste, and possibly for fertilizer produced by that method. Your patent would essentially cover the technical breakthrough – of conceiving of its possible use in waste treatment, and of working out how to apply this in practice. You would not normally be able to patent the relevant bacterium as such, because it would already be a known thing – however, if you used genetic engineering to create a completely new bacterium that was especially useful for your application, this microorganism might be eligible for patent protection in its own right.

Just because you come up with this new idea, and worked out how to put it into practice, you are not automatically entitled to get patent rights. To get a patent, your method would need to be truly new or novel (it would not be novel if you or someone else had already published a report on waste treatment using these bacteria before you tried to get a patent). Your method would also have to be more than an obvious thing to do based on the general background of technology (for instance, if it was already known that a very similar kind of bacteria was useful in achieving the same objective, and people working in the field would routinely turn to your bacterium when trying to solve this problem).

Your invention would also have to be genuinely useful in achieving the benefits you claim for it – you might not get a valid patent if you claimed patent rights over a wide range of bacteria, when only a few bacteria within that scope actually worked properly. You might also need to address concerns that exploitation of your method was not harmful to the environment, and was consistent with public order and morality.

Conditions for patentability

Not every new product or research outcome qualifies as an 'invention.' And it's not enough just to have created an 'invention' to be eligible for a patent. It has to be an invention that passes certain legal tests – the tests for 'patentability.' So the patent law of most countries includes three basic criteria for determining whether a claimed invention is eligible for a patent. These are termed the conditions for 'patentability.' The TRIPS Agreement expresses these conditions in a way that is now widely used in national laws. TRIPS specifies that patents should in principle be available for any inventions, whether products or processes, provided that they are:

- new (or 'novel');
- involve an inventive step (or are 'not obvious'); and
- are capable of industrial application (or have 'utility').

These requirements were only spelt out in a fully international treaty for the first time in the TRIPS Agreement, but they were already common to almost all national patent law in some form, and overlap with the underlying definition of 'invention.' These requirements have been applied in one way or another over centuries of patent law, in order to limit the application of patents to those particular kinds of invention which have the potential of introducing a tangible benefit to society. As a result, not all 'inventions' are patentable. These requirements are discussed in more detail in *Module Two: Biotechnology and Intellectual Property*.

Patent law often provides for exceptions to the kind of subject matter that can be covered by patents ('patentable subject matter'). These exceptions relate to material that might be a patentable invention (meeting the general criteria for patentability), but which are still excluded as appropriate subject matter for patents. This is usually due to a legislative decision not to extend patent protection to certain specific classes of subject matter out of concern for other policy objectives. For example, TRIPS provides for exclusions from the scope of patentable subject matter:

> Members may exclude from patentability inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect *ordre public* or morality, including to protect human, animal or plant life or health or to avoid serious prejudice to the environment, provided that such exclusion is not made merely because the exploitation is prohibited by their law.

TRIPS also gives the option of excluding other forms of subject matter from patentability:

(a) diagnostic, therapeutic and surgical methods for the treatment of humans or animals;

(b) plants and animals other than micro-organisms, and essentially biological processes for the production of plants or animals other than non-biological and microbiological processes.

For example, a country could decide that, even though a new surgical method was an important invention, and it was new, had an inventive step and was useful under its patent law, it would still not grant patent protection to that invention. There may be policy concerns that patents on surgical methods could delay or impair the delivery of medical treatment, and the legislators might decide that these considerations outweigh the benefits of patent protection in this area.

DIFFERENT APPROACHES TO PATENT EXCEPTIONS

As a result of differing policy approaches to the scope of subject matter for patents, national patent laws express different requirements for patent eligibility. For instance, the Intellectual Property Code of the Philippines excludes the following from patent protection:

- Discoveries, scientific theories and mathematical methods;
- Schemes, rules and methods of performing mental acts, playing games or doing business, and programs for computers;
- Methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practiced on the human or animal body. This provision shall not apply to products and composition for use in any of these methods;
- Plant varieties or animal breeds or essentially biological processes for the production of plants or animals. This provision shall not apply to micro-organisms and non-biological and microbiological processes.
- Aesthetic creations; and
- Anything which is contrary to public order or morality.

The People's Republic of China's 1992 Patent Law currently specifically excludes patents on:

- Scientific discoveries;
- Rules and methods for mental activities;
- Methods for the diagnosis or for the treatment of diseases;
- Animal and plant varieties;
- Substances obtained by means of nuclear transformation.

The law of the Republic of Korea provides that 'inventions liable to contravene public order or morality or to injure public health shall not be patentable.'

This kind of provision (which is found in similar forms in most national patent law) specifies that even if an invention meets all the necessary standards – for example, even if a method of medical treatment is an invention which is truly novel, has a clear inventive step, and is definitely useful, it could still be denied patent protection for broader policy reasons.

What rights does a patent give?

Patent rights are limited, exclusionary rights. That is, they permit a patent owner to exclude others from making use of, or producing the claimed invention for a limited time, especially in a commercial context. This does not necessarily exclude the use of the patented invention for research or educational purposes, use by the government, or use in the context of public need, such as in a national emergency. The patent right is not a positive right - it does not necessarily entitle the patent owner to carry out the invention. For example, if you invented and patented a new pharmaceutical treatment to cure diabetes, you would still need to go through the normal regulatory approval required for any new drug before you could sell the pharmaceutical. If you invented a new explosive compound, you could not make or sell the explosive if this contravened industrial safety laws. Or if you are granted a patent on a seed for a genetically modified crop, this doesn't entitle you to sell the seed or commercially farm it, as the patent right does not overrule any environmental, health or consumer protection laws that can forbid

or regulate your use of the crop. In short, if you are granted a patent for an invention, this does give you the right to prevent others from commercially using your invention - but it doesn't automatically mean that you can use it commercially yourself.

TRIPS has to some extent harmonised the nature of the patent right, specifying that a patent on a product gives the right to prevent others from the unauthorized making, using, offering for sale, or selling the product, and from importing for those purposes. It provides for similar rights relating to patented process and products obtained directly by that process.

Patent rights are *territorial* – they are granted by national authorities with application in the national jurisdiction only. There is no such thing as a 'world patent.' A Canadian patent has no legal effect in Malaysia, and a Malaysian patent has no effect in Canada. So a Malaysian business can make free use of a technology described in a Canadian patent if there is no corresponding Malaysian patent right. (They would need to check whether other IPRs might apply – including earlier patents with broader scope, or other rights such as plant breeders rights, copyright or design protection.)

For more detail about how researchers and their commercial partners can benefit from IP rights please see: *Module Ten: Case Studies on Commercialising Research*. Patent rights do not guarantee the commercial success of an invention but they can assist. Patent rights do not automatically guarantee that a patent owner can use their invention. For more information on this matter see the section on "Freedom to Operate" in *Module Eight: Researching and Intellectual Property Rights*.

Patents and technology disclosure

Disclosure of inventions is at the heart of the patent system. Patent rights are granted to inventors to encourage research, development and innovation in industry. The patent protection only lasts for a limited time, normally set at 20 years. In return for these time-limited rights, the inventor must disclose details of how to work the invention so that it can be freely used by the public at the end of the term of the patent. It also normally means that other researchers can use the invention in their research, and that the invention is available for educational purposes, even while the patent right is still in force. This technical disclosure – a description of how the new technology can be put into practice - is provided in a patent specification.

These specifications are lodged at patent offices as part of the patent application, and are normally made available to the public 18 months after the application is filed. These specifications are an invaluable source of technical information. Patent offices are increasingly putting this information in electronic databases, and it is now possible to access much of this data directly by the internet.

TRIPS clarifies that the obligation to disclose the patent is a firm international standard. It requires that an applicant for a patent must disclose details of their invention. This disclosure must be clear and complete enough to enable the invention to be carried out. TRIPS also indicates that national patent laws can also require that a patent applicant should indicate the best mode for carrying out the invention known to the inventor. In line with this, patent laws generally require a detailed technical description of an actual functioning product or process that embodies the invention.

How do you get legal protection for patents?

Patents are granted through the national patent office, such as the Indonesian Directorate General of Intellectual Property Rights, the Mexican Institute of Industrial Property, IP Australia, the US Patent and Trademark Office, or the Japanese Patent Office. The process normally requires lodging an application accompanied by a detailed description of the invention, and a fee. The application process for patents is discussed in *Module Three: Reading a Biotechnology Patent and the Patent Process*. Under various regional arrangements, a regional authority grants patents with legal effect in participating countries: these systems are currently available in Europe, Eurasia (covering many countries of the former Soviet Union), and Africa.

Because patent rights are part of national law, and apply only in the country where they are granted, you have to apply separately for each individual country where you want to protect your invention (or in the regions where a regional system exists). You then have to comply with each country's or region's patent process to receive a patent. The Patent Cooperation Treaty (PCT), discussed below in more detail, allows for an international application to be made for a patent in different countries – this system simplifies the initial application process and reduces formalities, but doesn't replace the eventual need for individual national or regional patents.

Individual countries (and in a few cases, regions) grant patent rights which only apply to their own jurisdiction. So if you discover a US, Japanese or European patent which is not registered in your own country, you can legally make use of the patented invention in your country (and anywhere else where the same invention is not covered by a valid national patent), free of any legal constraint. You could, for example, make and sell a patented product for your own domestic market and for export markets, provided only that you did not export the patented product to one of those countries where the patent is in force.

Who owns patent rights?

Patents are registered in the name of their owners (often described as the 'patentee,' 'patent holder' or 'assignee'). This could be the inventor, but is often another person, company or institution.

An inventor can apply for a patent and if their application is successful they will be the patent owner. However, the individual inventor generally doesn't own the patent that is granted on their invention. This can occur if an inventor who is also the patent owner decides to sell the rights to the patent and assigns the rights to the purchaser. More frequently, the patent concerns an invention made by an employee in the course of their duties. A lot of research is conducted by employees who use the facilities of their employers. The general rule is that an invention made by employees in the course of their normal duties becomes the property of the employer, unless there is explicit agreement to the contrary. This issue arises, for instance, in relation to employee researchers in research institutes, universities and corporate research organisations. To avoid dispute over who owns the inventions created by employees, employment contracts often provide for employers to own the inventions created by their employees. If an employee wants ownership rights over their invention they usually would need to negotiate with their employer for such a right. However, the patent law of a number of countries provides employees with an entitlement to specific rewards in recognition of the economic benefits of their invention. *Module Eight: Researching and Intellectual Property Rights* looks at some of the issues that are relevant to the researcher.

How long do patent rights last?

The term of protection for patents is limited – in most cases, it runs for 20 years from the date the application is filed with the patent office. But the grant of a patent does not mean that it will automatically stay in effect for a full 20 years. In most countries, patent offices require regular fees to keep the patent in force, and these fees often rise during the life of the patent. When maintaining patents is not commercially viable, then many patents lapse due to the non-payment of fees and therefore fall into the public domain much sooner than the 20 years. Another reason for not paying regular fees is that the patented technology may soon become outdated and obsolete, and it is simply not worth continuing to pay for the patent. A change in company direction, or liquidation, can lead to patents being abandoned. In some cases, patents can also be partially or fully cancelled as a result of legal challenge. In general, don't assume that a patent has legal effect – before making any major decisions based on the apparent existence of a patent right, you should always check its current legal status to see whether it has lapsed or been cancelled. Some countries allow for extensions to the term of patents when there has been a long delay in bringing the patented invention – this arises especially for pharmaceuticals. Because of the length and rigour of testing and approval processes for new pharmaceuticals, the patented product might only reach the market place late in the life of the patent, so that some extension of this term is considered justified.

PLANT BREEDERS' RIGHTS

Plant breeders' rights (PBRs) give plant breeders the right to protect new varieties of plants – so you may also see them described as plant variety rights (PVR). These rights are distinct from patent protection, and are focused on the specific needs and interests of the plant breeding and propagation process, originally based on traditional plant breeding methods. The nature of the protected subject matter and the scope of the right itself are therefore linked to the specific nature of plant breeding, and the way plant varieties are exploited. The protection only applies to new plant varieties as such, which are generally defined as the lowest level of taxonomy (or classification) within the plant kingdom – that is, plant varieties are distinct variations within a given species.

Specific plant breeders' rights date back to 1930 when they were first granted in the US under the Plant Patent Act (although US plant patents are significantly different from most plant breeders' rights systems). Subsequently plant variety rights systems were created in other countries, as a form of protection separate from the patent system. Proposals for international harmonization of these systems culminated in the negotiation, in 1961, of the International Convention for the Protection of New Varieties of Plants (the UPOV Convention). The UPOV Convention is not a system of legal protection in itself, but an agreed level of harmonization and cooperation between national authorities. For instance, the UPOV Convention provides that rights over a new plant variety should include certain exclusive rights over the propagating material of the protected variety. Seeds of a new variety are an example of propagating material. The UPOV rights include rights over the production, reproduction, sale, export and import of propagating material for protected plant varieties.

The TRIPS Agreement only provides very general obligations in relation to the protection of new plant varieties. TRIPS requires that plant varieties must be protected by patents, or by a separate 'sui generis' system, or by both. (A *sui generis* system is an individual system for a particular purpose – unlike the patent system which covers general technology. Another *sui generis* IP system is the specific protection of integrated circuit layout designs.) TRIPS does not directly specify what the *sui generis* alternative needs to look like. Most countries have adopted some form of PBR or PVR system along the lines of the UPOV Convention, although this is

not specifically required under TRIPS. Some countries allow for dual patent and plant breeders' rights protection while other countries do not. Some commentators have explored alternative possibilities for *sui generis* plant variety rights, although in practice, systems based on the principles of the UPOV Convention are common in developed and developing countries.

What is protected by plant breeders' rights?

PBRs or PVRs protect a new plant variety. In the UPOV system, eligible plant varieties must be:

- distinct from other varieties;
- uniform (i.e. a single crop of the new variety must demonstrate the same characteristics); and
- stable (i.e. subsequent plantings of the variety must demonstrate the same characteristics as the parent crop).

These requirements are usually summarized as the 'DUS' requirements (an acronym for Distinct, Uniform and Stable.)

EXAMPLES - PLANT BREEDERS' RIGHTS PROTECTION OF A NEW VARIETIES OF FRUIT

The Japanese National Institute of Agrobiological Resources, Tsukuba, Japan, applied in Australia in 1997 for plant breeder's rights on a variety of the Japanese Pear (*Pyrus pyrifolia*), called Gold Nijisseiki. Protection for this variety had already been applied for in Japan, the USA, New Zealand and the Netherlands.

The detailed description of this variety that was prepared in the course of the application and published for public scrutiny described the origin of the variety: '*Gold Nijisseiki* was bred through deliberate mutation of nursery stocks of the variety *Nijisseiki* and selected for strong resistance to black spot disease.' It then describes how its properties compare to those of the 'closest comparator,' namely the original variety Nijisseiki. It shows the results of field tests on resistance to black spot disease as:

Gold Nijisseiki	0% fruits infected	5-7% leaves infected
Nijisseiki	58% fruits infected	90% leaves infected

The official publication of this application also includes a colour picture of the two varieties showing their respective resistance to Black Spot. The resistance to this disease is one aspect of the 'distinct' quality of the new variety. This property of disease resistance would have to appear uniformly across a multiple crop of the pear, and would have to appear stably in successive generations.

Another system for protecting new plant varieties is the United States 'plant patent' system. US Plant Patent number PP008983 covers the banana plant known as FHIA-01, in the name of the *Fundacion Hondurena de Investigacion Agricola* (The Honduras Foundation for Agricultural Research). The new banana plant is described as having the following advantages over existing plants (with particular reference to an earlier variety known as Cavendish):

- High level of resistance to both the yellow Sigatoka leaf spot disease (Mycosphaerella musicola) and the black Sigatoka leaf spot disease (Mycosphaerella fijiensis).
- Practical immunity to both races 1 and 4 of Panama disease (Fusarium oxysporum f. sp. cubense).
- A strong root system, which makes it a hardy plant under marginal water and soil conditions.
- Cold tolerant - plant remains green under cold conditions which cause the reference "Williams" Cavendish variety to turn a yellowish color.
- Excellent green life of fruit after harvest which renders it suitable for export.
- Sliced or diced green and ripe fruit does not oxidize to an unsightly brownish color as does the fruit of the Cavendish export clones.
- Pleasant slightly tart flavor when ripe.
- Peel of harvested green fruit turns yellow when left to ripen under ambient conditions without ethylene treatment.

How do you get legal protection for plant breeders' rights ?

Like patents, PBRs are granted through a central registry, normally a dedicated plant breeders' rights office. A breeder seeking PBRs is required to lodge a specification to establish the distinctiveness of the plant variety being claimed. Colour photographs of the new variety may be included in the specification. Details of actual trials are also usually required. Further, there may be a requirement to conduct an independent trial specifically to determine whether the claimed variety meets the DUS criteria.

How long does plant breeders' protection last?

Like most intellectual property, the term of protection for PBRs is limited. UPOV provides that the term of protection is 20 years for all plants except trees and vines, which are considered more difficult to commercialise in a limited period.

More detailed information on this topic is available in *Module Seven: Plant Breeders' Rights*.

TRADE SECRETS

What is protected by trade secrets law?

Trade secrets are information of a business or technical nature that have commercial value and have been kept confidential. They can include secret processes, mixtures of ingredients, recipes, know-how or any other confidential information that may give a competitive edge or may otherwise be valuable. TRIPS requires that there be some form of legal mechanism available to stop the disclosure and unfair commercial use of information which:

- is secret in the sense that it is not, as a body or in the precise configuration and assembly of its components, generally known among or readily accessible to persons within the circles that normally deal with the kind of information in question;
- has commercial value because it is secret; and
- has been subject to reasonable steps under the circumstances, by the person lawfully in control of the information, to keep it secret.

Example – trade secrets protection for a food processing method

Say you have developed a new method for snap-freezing and thawing bananas so that they can be enjoyed fresh without discolouring and loss of texture. It may be an obvious application of an existing technology with some minor adjustments that cannot be patented (e.g. if a technology is already in use for another fruit such as the mango, and you make fairly obvious adjustments to it to make it work for bananas). Or you might decide the cost of patenting is too high and you believe you can commercialise your new method without revealing it to your competitors. But if you published an advertisement describing your method, or demonstrated your method to a group of banana farmers or potential investors, then you would not normally be able to stop other people from taking this method and using it for themselves, without any compensation or payment to you.

On the other hand, if you told your business partner or a potential investor about your new method, or demonstrated it to them, and this was done in strict confidence, so that they clearly knew they had an obligation to keep the information confidential, then the method could be protected by trade secrets law. You could even commercialise your method and use it for many years to process and distribute bananas, provided other people outside your business can't see how it works. There are several drawbacks. This form of protection depends on you taking the effort to keep the method secret. It also only extends to those to whom you disclose the method in secret. If someone else figures out how to use your method (e.g. by analysis or reverse engineering), and they developed their ideas independently of you, then they may make full commercial use of the method without owing you anything. What's more, if your method is still secret then the other person who independently came up with the idea may be able to get a patent.

Technology is often protected as a package of different rights. If your method for processing bananas was a significant technological breakthrough, then you might get a patent for the basic technology. But in using your method, you might develop further techniques for making it more cost effective, for instance in reducing the cost of refrigeration. These additional techniques may simply be know-how, not patentable in themselves, but could still be protectable as trade secrets.

From society's point of view, the patent system has been developed to encourage disclosure of inventions, so that there is an incentive to turn away from the kind of excessive use of trade secrets or confidentiality that might hamper the transfer of technology and the sharing of benefits from new technologies.

What material is protected by trade secrets law?

There are two general ways of protecting trade secrets, corresponding to the two main legal traditions – the common law tradition of the UK, the US and most Commonwealth countries, and the civil law tradition of continental European countries and those countries influenced by their legal systems. Under the common law approach, there is a general kind of legal action for breach of confidence – this gives you the right to take action against people who fail to honour an agreement with you to keep information in confidence – or who otherwise fail to live up to a relationship of trust relating to the information (for instance in exploiting the information for commercial benefit when it was only disclosed for preliminary evaluation). This form of legal action is part of the general background law within the common law tradition, and is not necessarily contained in specific legislation passed by the government. But many countries in the civil law tradition do have specific legislation, or statutes, that make it illegal to infringe trade secrets.

Trade secret protection or protection against breach of confidence is not limited to high-tech know-how. For instance, in Australia it has been used as a legal remedy against the unauthorized public disclosure of information, which was secret and sacred within the traditions of the Indigenous Pitjantjatjara people, when the disclosure was considered prejudicial to their culture and society.

How do you get legal protection for trade secrets?

TRIPS has a general requirement on governments to put in place some for of legal mechanism that enables action to be taken when trade secrets (or 'undisclosed information') are abused. But it leaves it up to national laws to determine how this happens. So countries use variations of the common law system, or have specific legislation, to define and protect trade secrets. Often, the protection of trade secrets is part of the general law against unfair commercial practices or unfair competition. These different systems do have common features. Generally, it is not necessary to register a trade secret to get protection for it (although it normally should be well documented). If someone later thinks of the same idea independently you have no rights against them and cannot stop them from using the idea. Also, if someone who has no connection with you can work out how your product was made simply by analyzing it ('reverse engineering'), then they are free to use that information to produce a competing product.

Trade secrets often constitute much of the valuable background knowledge that makes it possible to carry out a patented invention. It can, for instance, relate to a lot of the hard-won practical knowledge about fine-tuning a patented process to ensure that it operates most efficiently, and is better integrated with other manufacturing processes. It also relates to valuable commercial information, such as marketing plans and commercialisation strategies. So trade secrets or know-how often constitute a significant portion of the 'intellectual capital' that characterizes a successful enterprise.

Nonetheless, there is reluctance in some jurisdictions, especially common law countries, to recognize trade secrets or confidential information as a form of property in its own right, even though it can be sold and licensed. For example, the Canadian Supreme Court (R v. Stewart, 85 NR 171) concluded in 1988 that:

> It appears that the protection afforded to confidential information in most civil cases arises more from an obligation of good faith or a fiduciary relationship than from a proprietary interest. No Canadian court so far has exclusively decided that confidential information is property, with all the civil consequences that such a funding would entail.

Generally speaking, reliance on trade secrets is less legally certain, more unpredictable a tool for managing technology, and less transparent for the public than the patent system.

The two different systems for trade secret protection

Hong Kong, China and the Republic of Korea are good examples of the contrasting approaches to protecting trade secrets. Hong Kong, China, described its common law legal system to the WTO TRIPS Council as follows:

> Protection for undisclosed information is provided by the common law action for breach of confidence. The leading case is *Coco v Clark [1969] RPC 41,* where it was held that three elements had to be proved for a claim of breach of confidence to succeed: (i) that the information was of a confidential nature; (ii) that it was communicated in circumstances importing an obligation of confidence; and (iii) that there was an unauthorized use of the information.
>
> Hong Kong courts have interpreted the second requirement as fulfilled not only where the originator of the information has communicated the information to the defendant in confidence, but also where a third party has come by the information, and it is considered that he must, from the nature of the information, have realized that he was not entitled to use it. (*Dr Lam Tai Hing v Dr Koo Chi Ling, Linda* [1993] 2 HKC 1).

An example of specific trade secrets legislation is the Republic of Korea's *Unfair Competition Prevention and Trade Secret Protection Act* which has this specific statutory definition of trade secrets:

> Trade secrets shall mean production methods, marketing methods and other technical or management information useful for business activities which are not publicly known, have independent economic value, and have been maintained and managed as secrets through considerable efforts.

This law also specifically defines a wide range of activities as being in infringement of trade secrets, for instance acquiring trade secrets by theft, deception, coercion or other improper means, and provides for legal penalties

Who owns the rights in trade secrets?

Trade secrets are not protected as property at common law but the person whose secret has been disclosed or used can sue for breach of confidence. Statutory regimes provide that the owner of the trade secret is the person who developed the trade secret.

How long do trade secrets rights last?

Unlike patents and copyright, the term of protection for trade secrets is not limited. The legal protection of trade secrets can last indefinitely or until the 'trade secret' is made public. From society's point of view, trade secret protection can be less desirable than patenting, because by its very nature a patent requires the inventor to make available to the public a full explanation of how the invention works, so that understanding about the patented invention immediately passes into the public domain.

TRADE MARKS

What is a trade mark?

A trade mark is a sign used to distinguish goods or services in the market place from the goods or services of another trader. The trade mark can appear directly on the product (such as on a label on a bottle), in its packaging and other material (such as on a box or bag the product is sold in, and on instructions, guarantees and other documents), and in advertising and promotional material (for example, on a billboard or magazine advertisement). The actual shape of a container can be a trade mark – the shape of the famous COCA-COLA bottle is itself a trade mark in a number of countries. When a trade mark is used in the services sector (for example, banking, pathology services, internet or telecommunication services), the trade mark is used in association with the provision of services (on signs at an office or workshop, for instance, on documentation such as quotations, invoices and reports, or on a website offering or providing the service), and on promotion material (such as advertisements).

The main legal property of a trade mark is that it should effectively function as a sign that shows that a certain product is associated with one business in particular. How a trade mark works depends on the nature of the word or other sign in a particular sector of commerce. For example, the word APPLE is a distinctive trade mark for computer products in many countries – and it would be misleading for a non-APPLE computer or computer component to be sold under that trade mark, because a consumer would probably assume that a computer marked with that trade mark came from the well known computer company, or was somehow endorsed by that company for use in their computers. But in the food business – for example, for fruit juices or confectionery - the word 'Apple' is needed to describe a fruit and its flavour. A company could hardly sell 'Apple' fruit juice and claim that this was a distinctive trade mark. It would be

wrong to grant anyone exclusive rights to use the term. For this reason, the rights associated with a trade mark are linked to particular goods and services, and do not normally extend to other areas of commerce – it is not unusual for the same trade mark to be used by different businesses operating in completely different lines of business. For instance, "Prince" is a trade mark owned by at least two completely separate businesses, one producing sports equipment, the other providing information technology services.

TRIPS provides that any sign capable of distinguishing the goods or services of one undertaking (eg, an individual merchant, a company, or a cooperative) from those of others shall be capable of being a trade mark including personal names, letters, numerals, figurative elements and combinations of colours. Some countries extend the scope of the definition of trade mark, and allow for trade mark protection to cover distinctive sounds and smells, as well as the shape of the product itself or its container.

Example – trade mark protection for different products

The words TIGER BALM are registered as a trade mark in Australia for 'Medicinal and medicated preparations for human use' (registered trade mark 470186). The word 'tiger' is used in many other unrelated trade marks for other goods and services, so that the TIGER BALM trade mark would not create an unlimited right to prevent other businesses from using 'tiger' and images of tigers for other products. In the rather specialized field of medical preparations for tigers and veterinary medicine, the words 'tiger balm' may also need to be kept as a descriptive term for treatments that are specifically useful for treating tigers.

The word GARUDA is registered as a trade mark in Australia for a wide range of goods and services, including printed matter, games and playthings, model aircraft, travel insurance, money exchange, aircraft repair and maintenance, transport, travel arrangements, travel agent services, entertainment, cultural activities, training services, and provision of food and drink, accommodation (trade mark 821268), in the name of the well-known Indonesian airline company. But the same word, GARUDA, is also registered as a trade mark in relation to preserved, dried and cooked fruits and vegetables, and prepared nuts, in the name of a different company which may be unrelated (trade mark 711 937). The national emblem of Indonesia also includes an image of the garuda, which is a mythological bird in Indian and Indonesian culture. This may limit the use of particular images as trade marks, as it is an international standard that notified national emblems should not be used or registered as trade marks.

How do you get legal protection for a trade mark?

There are two distinct forms of protection. The most transparent and predictable way of protecting trade marks is through official registration at the national trade mark office – similar to registration of patents and PBRs. This is the preferred approach of most enterprises. But, unlike patents and PBRs, you do not have to register a trade mark for it to be protected by law. Rights to a trade mark can arise through use. In the example of snap-frozen bananas cited above, if you sold the bananas under the trade mark 'Brilliant Bananas' you would have the choice of trying to register 'Brilliant' as a trade mark in respect of fruit, or simply making use of the trade mark to build up a distinctive reputation in the market place over time, in the hope that you would be able to defend your interests if someone else tried to cash in on your reputation by representing their product as Brilliant Bananas.

What's the difference between registered and unregistered trade marks?

Both registered and unregistered trade marks are associated the reputation of the trader in respect of specific goods and services. The signs ® and ™ are often used together with a trade mark. ® indicates that the trade mark is registered, and should only be used in connection with a registered mark. ™ indicates that the word or sign is presented as a trade mark rather than as a descriptive or other term, but it need not be registered – for example, you could sell your snap-frozen bananas as Brilliant Bananas™ to indicate that the term is being used as a trade mark. ℠ can be used similarly for a 'service mark' – a trade mark used in respect of services.

Advantages of registered trade marks are that the protection dates from the application for registration and they can be easier and cheaper to enforce than unregistered marks. Also, registration may last indefinitely and the protection tends to be for a whole country not just a smaller area.

Advantages of unregistered trade marks are that there is no need to go through the registration process and no registration fees are payable. But it can be very difficult to enforce rights in an unregistered trade mark, as it's necessary to build up strong evidence that the public sees the word or symbol in question as a trade mark. Some marks are initially not registrable because they are not considered sufficiently distinctive. Clearly you couldn't claim as your trademark for your bananas 'Yellow Bananas' or 'Fresh Bananas' because these are descriptive terms that anyone should be free to use. In other cases, it is difficult to draw the line. For example, you might try to register 'Brilliant Bananas' as a trade mark, and this could be accepted because it is sufficiently distinctive, or it could be rejected on the basis that the word 'brilliant' should be available for any trader to use as a descriptive or laudatory term for the bananas they are trying to sell. Even if you failed to register the mark 'Brilliant Bananas,' this mark might nonetheless be important to the reputation of your business. Unregistered marks can be protected by unfair competition laws – if someone else uses an unregistered mark, this can be considered misleading or deceptive commercial conduct. In addition, if you used 'Brilliant Bananas' as a trade mark for several years, and you can prove that it has become distinctive in the fruit trade, then you might be able to register it subsequently on the basis that it has become distinctive through use.

What rights are associated with trade marks?

A registered trade mark right is infringed if a person uses in a particular commercial context a sign that is substantially identical to or deceptively similar to the trade mark for the promotion of similar goods and services to those protected by the trade mark. In essence, the trade mark registration can be used to prevent other people from using a similar sign on goods or services that suggests some form of connection with the owner of the registered trade mark. It generally can't be used to stop use of a similar trade mark in a completely different line of business (see the examples above). When a trade mark is considered 'well known' or 'famous,' the scope of the trade mark right is broader.

TRIPS provides for exceptions to trade mark rights such as fair use of descriptive terms if such exceptions take account of the legitimate interests of the owner of the trademark and of third parties.

How long do trade mark rights last?

TRIPS provides that initial registration and each renewal of registration of a trade mark shall be for a minimum of 7 years. The registration of a trade mark can be renewed indefinitely, and some trade mark registrations (such as 'Kodak') have been in force for well over a century. If a registered trade mark is not actually used or ceases to be used, then someone else may reasonably wish to use it. For this reason, a registered trade mark can generally be removed from the register after a certain delay if the trade mark owner has not used it or has stopped

using it. This is to ensure that unused or abandoned marks do not remain on the trade mark register when they conflict with other traders' legitimate interests. TRIPS provides that 'if use is required to maintain a registration, the registration may be cancelled only after an uninterrupted period of at least three years of non-use, unless valid reasons based on the existence of obstacles to such use are shown by the trademark owner.'

Similarly if a trade mark becomes generic, that is it becomes commonly identified for a general purpose, then it may lose its distinguishing characteristic and cease to be a trade mark. For example Xerox was registered as a trade mark for electro-photographic copying machines and apparatus for fusing powder images in 1952, and was used widely for these kind of copying technology. This reached a point by the 1970s that the trade mark almost became a generic descriptive because many people referred to photocopiers and photocopying as xerox machines and xeroxing. Other trade marks such as 'Velcro' and 'Hoover' have similarly been in danger of losing their distinctiveness. Linoleum is now the standard descriptive English word for a form of flooring material originally made by coating canvas with oxidised linseed oil. This term was originally a trade mark in the name of the Linoleum Manufacturing Company (and linoleum flooring was also patented), but it is now a generic term which any manufacturer can use for their product.

INDUSTRIAL DESIGNS

The industrial design system protects the distinctive appearance of products – it only protects the look of items, and not how they function or the underlying technology. So if you had design protection for a new kind of folding chair, your rights would only extend to chairs that looked like your protected design, not chairs that folded in the same way. Protection is given to distinctive ornamental or aesthetic elements of the product. To be eligible for protection, a design has to be new in appearance, although this can include relatively minor variations on existing designs. There is no need for the kind of 'inventive' or 'useful' qualities that apply for instance to patentable inventions. All that is required is that the design should differ in the way it looks from previous work in that area.

Under the TRIPS Agreement, protection has to be available for 'independently created industrial designs that are new or original,' and indicates that designs may not be 'new or original' if they 'do not significantly differ from known design features.' TRIPS also provides that protection need not be extended to designs which are purely dictated by 'technical or functional considerations.'

Designs can cover a very wide range of products, such as handicrafts, furniture, electrical appliances, food containers, textiles, clothing, toys and building materials. The industrial designs system is often very useful for middle-level innovators, including small or medium enterprises, which create innovative products that are not necessarily technological developments, but are nonetheless commercially valuable new products.

While not directly applicable to the products of biotechnology, design protection may be useful in product development in this field, as it can protect the distinctive appearance of products such as diagnostic kits and analytical tools. For example, Australian registered design AU 137103 S protects the features of shape and/or configuration of a 'point of care diagnostic device' produced by the Adeza Biomedical Corporation, and registered design AU 142947 S, held by the company Human GmbH, protects the appearance of a human midstream pregnancy test.

In the US, industrial designs are protected through design patents. Following is an example of a US design patent claiming 'the ornamental design for a device for chemical analysis of foods and other substances.' Along with the claim and other details of the individuals and company which created the design, there are eight drawings illustrating the design, one of which is reproduced here.

US00D424457S

United States Patent [19]

Gordon et al.

[11] **Patent Number: Des. 424,457**

[45] **Date of Patent: ** May 9, 2000**

[54] **DEVICE FOR CHEMICAL ANALYSIS OF FOODS AND OTHER SUBSTANCES**

[75] Inventors: **Virginia C. Gordon; Bennett W. Root, Jr.**, both of Huntington Beach, Calif.

[73] Assignee: **Safety Associates, Inc.**, Tustin, Calif.

[**] Term: **14 Years**

[21] Appl. No.: **29/103,859**

[22] Filed: **Apr. 22, 1999**

[51] **LOC (7) Cl.** **10-04**

[52] **U.S. Cl.** **D10/81**

[58] **Field of Search** D10/81; 435/7.92, 435/7.1; 436/318; 422/56, 58, 102; 210/238

[56] **References Cited**

U.S. PATENT DOCUMENTS

D. 282,399	1/1986	Stafford	D10/81
D. 353,680	3/1995	Marks	D10/81
5,958,704	9/1999	Stazzl et al.	435/7.1

Primary Examiner—Antoine Duval Davis
Attorney, Agent, or Firm—Robert D. Buyan; Stout, Uxa, Buyan & Mullins, LLP

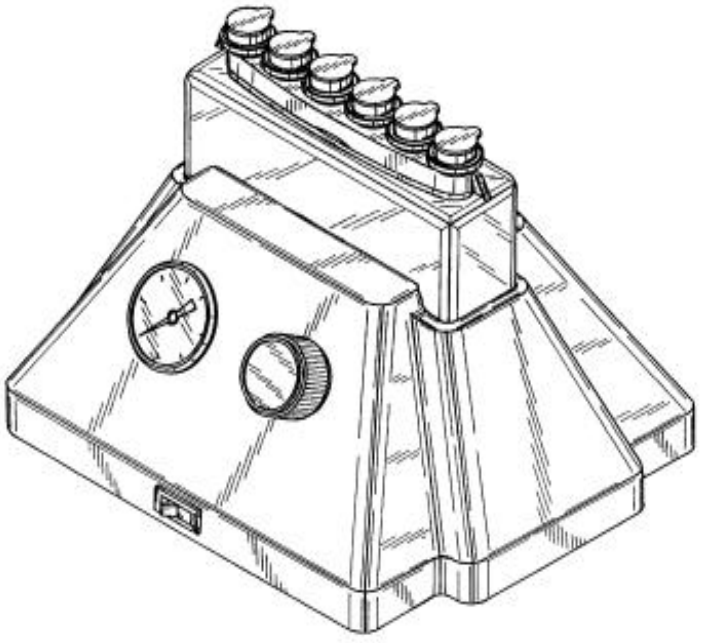
[57] **CLAIM**

The ornamental design for a device for chemical analysis of foods and other substances, as shown and described.

DESCRIPTION

FIG. **1** is a perspective view of a device embodying the design of the present invention.
FIG. **2** is a front elevational view of the device of FIG. **1**.
FIG. **3** is a top plan view of the device of FIG. **1**.
FIG. **4** is a left side elevational view of the device of FIG. **1**.
FIG. **5** is a right side elevational view of the device of FIG. **1**.
FIG. **6** is a rear elevational view of the device of FIG. **1**.
FIG. **7** is a bottom plan view of the device of FIG. **1**; and,
FIG. **8** is an exploded perspective view of the device of FIG. **1**.

1 Claim, 5 Drawing Sheets



COPYRIGHT AND RELATED RIGHTS

Copyright is concerned with the protection of original literary and artistic works – indeed, the French term for copyright is 'droit d'auteur' or 'author's right.' But what constitutes a 'literary or artistic work' is very broad, and goes beyond creative works or aesthetic works like paintings, songs, or novels. The Berne Convention, which is the principal international agreement on copyright, provides that:

> The expression "literary and artistic works" shall include every production in the literary, scientific and artistic domain, whatever may be the mode or form of its expression, such as books, pamphlets and other writings; lectures, addresses, sermons and other works of the same nature; dramatic or dramatico-musical works; choreographic works and entertainments in dumb show; musical compositions with or without words; cinematographic works to which are assimilated works expressed by a process analogous to cinematography; works of drawing, painting, architecture, sculpture, engraving and lithography; photographic works to which are assimilated works expressed by a process analogous to photography; works of applied art; illustrations, maps, plans, sketches and three-dimensional works relative to geography, topography, architecture or science.

TRIPS (and a later treaty, the WIPO Copyright Treaty) adds to this definition by specifying that computer programs (both in source or object code) shall be protected by copyright as literary works.

'Related rights' or 'neighbouring rights' describes a set of rights that are similar to copyright but do not directly involve rights to a work as such – these include the rights of performers (such as those singing or playing music), the rights of producers of sound recordings (separately from the musicians or songwriters), and the rights of broadcasting organisations. These rights are very important in some industries, but are of little relevance to the biotechnology field. However, copyright itself does have significant practical implications for researchers and commercial enterprises working with biotechnology.

Under copyright law, when you write a new article, a research report or a lecture, when you sketch a new diagram, or when you produce a computer software program, you automatically gain legal rights to stop others from reproducing or otherwise using this material – within reasonable limits.

If you write a commentary on recent developments in biotechnology and publish it in a journal or place it on a website, copyright gives you the right to stop other people from publishing it in another journal or placing it on their website without your permission. But copyright only covers the way you express your ideas, not the ideas themselves. TRIPS specifies that 'copyright protection shall extend to expressions and not to ideas, procedures, methods of operation or mathematical concepts as such.' So someone else would be entitled to publish a similar commentary covering the same ideas as yours, provided it was not a copy of your own publication. And copyright is not absolute – for instance, it would not normally be necessary to get your permission for someone to quote passages from your commentary in the process of reporting on your views, or preparing material for educational purposes.

Copyright is different from patent protection and the other forms of IP discussed in this module in several important ways.

- It doesn't need any formalities. There is no need to apply to a government office for copyright to be recognized. The legal right comes into being automatically when you produce the protected material. (But it's a good idea in practice to apply the symbol ©, the name of the author, and the date of publication to notify people that copyright does apply to the material, unless you don't mind if it's copied or published without reference to you.)
- It only covers actual copies of the protected material, not just material that happens to be similar to it or coincidentally resembles it. So if you draw a diagram or take a photograph, and later someone independently produces material that is very similar to yours – which

you feel takes the essence of your original work – your copyright wouldn't apply to their work. There would have to be a process of copying or reproducing your actual work. By contrast, if you have a patent on an invention, and someone who has no knowledge of your research work later comes up with technology that takes the key elements of your invention, you can still use your patent to prevent them from commercializing their later invention. There is no need for you to prove that they have directly copied from you – you just have to show that they have used all the elements of the claimed invention in your patent.

Much of copyright law is about who can reproduce protected material, how much, and for what purposes. It also applies to other ways copyright material is used – for instance, adaptation, performance in public (for instance of a song or a play), translation (such as translating a textbook from German to Thai), and making it available to the public (like uploading it onto the internet). Exercising your rights in copyright works doesn't necessarily mean stopping others from using or distributing your copyright material. Some researchers, teachers, or commentators are pleased to see their copyright material widely reproduced and distributed without expecting direct payment for this. But they may wish to ensure that they are acknowledged as the author of the works, and that the material is not altered or used inappropriately. You can use copyright can be used to ensure that your work is reproduced and used in suitable ways, even if you do not want to use your copyright for commercial gain.

There are, in any case, limits on the degree to which you can exert your copyright. Most national copyright systems allow for limited forms of copying so that copyright is workable and doesn't become too much of a burden for society generally – these exceptions to copyright typically relate to educational, archival and private non-commercial use, as well as for reporting news, criticism, parody and other uses. These exceptions are often referred to as 'fair use' or 'fair dealing' of the copyright work.

Copyright for researchers

For researchers and academics, copyright has mainly been of concern because their work involves use of published works – textbooks, journal publications, research outcomes. If you have written a textbook, you may be concerned that unauthorized copies of the textbook become used so widely that there is no market left for the authentic copies of the textbook – apart from reducing your royalties from book sales, this may affect the viability of publishing an updated or revised edition of the textbook, for example. On the other hand, teachers and academics generally have an entitlement under copyright law to make photocopies or digital copies of some portions of a textbook or journal article for use in education. Copyright establishes the rules that apply to this sort of educational use of written material – generally, there's an attempt to balance the reasonable interests of the author or publisher with the public interest in having copyright material freely available for education, research, criticism and commentary. There is obviously a big difference between copying a few pages from a textbook and circulating them to your class for reference during a lecture or seminar, and making multiple copies of the complete textbook and selling them commercially. Copyright tries to draw the line between these two extremes.

Recent developments have broadened the scope of copyright that scientific researchers and academics need to deal with, including in the biotechnology field. For instance, computer software, both in source code (programming language) and object code (machine language) is now protected by copyright, as though it were a literary work. This applies to standard word processing packages, operating systems and spread sheets, for example, as well as specialist research and analytical software, so that making unauthorized copies of these programs for widespread distribution counts as a breach of copyright.

A second area where copyright can also be used to protect collections of data, such as a database of gene sequence listings – even if the individual data are not subject to copyright, copyright can protect the effort that is involved in compiling and assembling the data, provided this compilation amounts to a distinct work – in the words of TRIPS, compilations of data or other material are eligible for copyright material when 'by reason of the selection or arrangement of their contents [they] constitute intellectual creations' in their own right. In addition, there have been proposals for international recognition of distinct IP rights in databases, quite apart from copyright – the European Union has already recognized database protection at the regional and national level.

The effect of IP rights on databases (whether through copyright or distinct database protection) is still an area of some uncertainty, but it looks to become an increasing practical reality for people working in the biotechnology field, with the emergence of bioinformatics as a distinct field, and the growth of genomic databases.

1.3 Enforcing intellectual property rights

Intellectual property rights can be very valuable commercial rights for inventors, creators and researchers. As discussed above, IPRs are usually exclusive legal rights to do certain things in relation to an invention or creation. In order to ensure that IPRs serve their intended purpose, there must be a way of ensuring that legal action can be taken when they are infringed.

TRIPS requires WTO Members to provide effective enforcement remedies. It refers to 'civil' and 'criminal' remedies. In civil cases, the person owning the IP right files a complaint against the person alleged to be infringing that right. A court hears the two sides of the case, and makes a judgement as to whether the allegation of infringement is true or not. If the court decides that the complaint is correct, and there has been an infringement, then it can order various 'remedies' or ways of stopping the infringement and compensating for the damage caused by the infringement. Civil remedies include:

- injunctions (i.e. use of a court order to stop the use of an infringing product or process);
- damages (i.e. paying costs of infringement to the right holder);, and
- account of profits (i.e. payment of profits made by the infringer to the right holder).

Civil cases are the normal way of dealing with patent disputes. In the criminal system, the state itself deals with the infringement. Police can seize goods which are believed to be infringements, and the public prosecutor initiates a case against the person alleged to be guilty of the infringements. This procedure is rare for patent cases, and does not exist in most countries. Criminal enforcement of IPRs is more frequent for trade mark and copyright infringement, when this occurs on a commercial scale.

Another way to enforce IPRs is to use customs services at the borders of countries to seize infringing IP material before it enters the country. TRIPS requires that border enforcement measures be available for trade mark counterfeiting and copyright piracy.

For more information on enforcement of IP rights refer to *Module Nine: Licensing and Enforcement of Intellectual Property Rights*.

1.4 IP & the lifecycle of a new product

From a practical point of view, it is important to see IPRs in an holistic way – in other words, not to focus exclusively on one particular kind of IPR as being relevant to you, while ignoring other rights. To illustrate this, we look at how different IPR come to play in the lifecycle of an hypothetical new research program, project Lambda:

RESEARCH PLANNING PHASE	• A search of existing **patent** documents is undertaken, to: • Identify potential competitors • Determine the state of the art in existing research • Find niche opportunities • Avoid duplication of research efforts • Undertake market research • Examine investment and technology trends • Locate potential research or commercial partners
RESEARCH PHASE	• **Confidentiality** and the law of **trade secrets** becomes important to safeguard: o Research directions and outcomes of project Lambda o Agreements with research partners o Confidentiality within the enterprise or institution • **Patent** law considerations are also essential in relation to: o Publications by those working on Project Lambda o Participation in trade fairs and scientific conferences
RESEARCH BREAKTHROUGH	• Any outcomes must be kept **confidential** at least until **patent** applications are filed • A **patent** filing strategy needs to be adopted o Including a possible choice to keep the outcome as a **trade secret** and not pursue **patents** at all • Associated developments may be protected as **industrial designs** • Associated software and documentation might be protected through **copyright**
DEVELOPMENT PHASE	• An IPR **licensing** strategy is required • **Trade marks** may need to be developed • An international **patent** strategy is required, underpinned by a commercial strategy • Patents may be required on improvements to the original

	breakthrough • **Cross-licensing** or other 'freedom to operate' strategies to gain access to overlapping IP owned by others if needed to allow the product to be commercially developed and put on the market
MARKETING PHASE	• The marketing strategy will need to consider effective strategies for protecting and promoting **trade marks and designs** • It is necessary to monitoring the marketplace for possible **infringement** and **enforcement** action • The portfolio of registered **patents, trade marks and designs** will need careful management • There will be continuing issues of **licensing** and **valuation** of the IP assets from Project Lambda

1.5 Why Have Intellectual Property Rights?

The IP system raises complex policy issues, and there has long been a debate about the desirable scope of IP protection. This generally concerns the tension between the need to promote and reward innovation, creativity and productive private investment, and the need to ensure freedom of expression, the flow of information and cultural works, and access to technology. The debate over the desirability or otherwise of the various elements of IPRs has been extensive, and is beyond the scope of this Handbook. However, some general comments are provided to stimulate your further enquiry and reflection.

The objectives normally put forward for recognition and protection of IPRs are:

- To contribute to the development of national economies by assisting to:
    - encourage and reward innovation and development;
    - benefit from international trade opportunities; and
    - attract foreign investment and technology transfer
- To comply with international standards; and
- To recognise an inventor's and creator's right to be recognised and rewarded for their intellectual endeavours.

Contribute to the Development of National Economies

The main value of IP laws is that they contribute to the development of national economies. Countries have IP laws to:

- enhance trade and investment in their country
- encourage technological development
- develop internationally competitive enterprises
- assist the effective commercialisation of inventions and innovations
- promote social and cultural development, and

- secure international reputation for exports.

A national IP system does not guarantee automatic national prosperity and trade advantages. A patent does not in itself make an inventor rich, but skilful use of the patent system can be one path to commercial success. An inventor cannot normally get the rewards of an invention without a patent. In the same way, few nations can create sustainable industrial growth and international competitiveness without an effective, well administered IP system. Yet it is vital to bear in mind that IP rights are not given as privileges or favours – they are recognised and granted to promote the community interest. This also affects how they are administered and exploited – some legal systems have specific penalties for misuse of the exclusive rights provided under the IP system. Achieving the benefits expected of the IP system therefore requires a suitable system of checks and balances, something that can be very difficult to achieve in practice.

Encourage and Reward Innovation and Development

The grant of IPRs to creators and inventors is intended to encourage research, innovation and development for the benefit of the community. It is intended to help them to benefit from their invention by compensating them for the work put into developing their product or process. It also gives an incentive to make the investment to turn an invention into a product ready for the marketplace. It can be a long process, moving from the original flash of insight that led to the invention, to a finished product, available for the consumer, that has been tested and proven to be safe and practically useful.

This incentive works by protecting the right holders from 'free riding' by their competitors. A free rider benefits from the work of others without bearing the cost of making a creative work or invention. By limiting free riding, IP laws encourage investment of finance and research efforts into longer-term outcomes.

In principle, IP laws aim to benefit industry, businesses and the community. Industry can benefit financially from patent protection for their inventions that often need large investments of time and money to produce. The community benefits from the availability of more creations and inventions. Businesses can use trade marks to protect their reputation and name and designs protect the appearance of their goods in the marketplace. These protections are important to protect the investment that business makes in developing and marketing goods and services.

Benefit From International Trade Opportunities

Trade liberalisation has increased the pressure on domestic industries to become more competitive against international benchmarks – this entails access to new technologies, generation of indigenous technologies, and other strategies for producing higher-value products. Also, the relative value of raw commodities has been steadily dropping for many years. Products need to be more distinctive to benefit from international trade opportunities, drawing on inventiveness, quality, regional characteristics, and the application of specialist or traditional skills. Businesses need to build up and safeguard a distinctive presence and valuable reputation in global markets.

IP rights are part of the 'added value' in trade – the move towards producing more distinctive products, and away from trading in raw commodities. Patents can be particularly important to high technology inventions. But IPRs also represent added value to trade in many other goods and services, as they can safeguard a wide range of innovations, distinctive local qualities, designs, reputations, and traditions.

Example: Coconut Cream Soap

IP rights are not restricted to the high tech sector. Traditional products have been effectively protected by IPRs, although many opportunities have been lost. More effective use of the IP system can generate higher rewards for traditional or low technology products. For example, imagine a company in Fiji wishing to produce a new product based on an existing tradition of producing coconut cream soap. It could strengthen its position in global markets by:

- protecting trade secrets or confidential information associated with the know-how used in processing the coconut and producing the soap;
- taking out patents to protect any specific new processes developed to process coconut oil and to produce the soap;
- creating and protecting trade marks to give the soap a distinctive identity in global markets – for instance, the soap could bear the trade mark LUCINA;
- copyright to protect pictures and writing on the soap's packaging and labeling and design protection for packaging and related accessories, for example drawing on Fijian traditional motifs;
- using certification marks to provide reassurance about particular qualities of the soap, for instance certifying the use of organic contents;
- geographical indications to strengthen the association in the minds of the consumer with the product's origin – for example, from the island of Vanua Levu; and
- breeders may also develop a new strain of high-yielding coconut especially useful for oil extraction and soapmaking.

Instead of soap exported as a basic commodity, valued by its weight, these forms of IP potentially combine to create a valuable product, in this instance: 'Lucina, Quality Fijian Coconut Cream Soap, made by the traditional methods of Vanua Levu, certified organic produce.' The product could be sold in a distinctive package using traditional Fijian designs.

In addition to enhancing the value of inventions and other merchandise, IPRs themselves can be traded in global markets. For example, imagine that a Fijian company had patented an efficient new process to produce coconut soap. The patent owners could license rights to use that patented process in countries all over the world. The international licensing of the patent right is an example of how IP rights in goods can be traded in global markets quite separate from the trade in the physical product, which in this example is the soap.

Attract Foreign Investment and Transfer of Technology

The effectiveness and scope of IP protection is reported to be one factor in establishing the domestic infrastructure that attracts productive foreign investment including the transfer of new technology. TRIPS is seen in practice as the principal international benchmark for a sufficient IP system.

Example - Pharm-Biotech and "BanDolor" capsules

For example, imagine that a private company called Pharm-Biotech is deciding where to base a new research and manufacturing facility in the Asia Pacific region. The factory will manufacture Pharm-Biotech's patented headache tablet called "BanDolor" and a range of other products. Pharm-Biotech intends to employ 100 local staff in its factory. Several countries are very keen to attract this foreign direct investment.

In developing an investment strategy, Pharm-Biotech is concerned to ensure that it can undertake the expensive steps of establishing a new manufacturing plant, undertaking extensive regulatory approval processes, training personnel (including passing on vital know-how and other skills) and investing in marketing, without the value of the investment being nullified by the emergence of copies of BanDolor. These copies could be poorly made, ineffectual or even toxic, with consequence negative impact on the future of the new product. Vital know-how may be unprotected, deterring transfer of this technology. The company's decision will be affected by many factors – the nature of the domestic market, the overall global marketing strategy, relationships with suppliers and other commercial and research partners, infrastructure, and other matters such as the taxation and foreign investment regime. However, in an industry such as pharmaceuticals, which is heavily dependent on IP protection for return on investment, the nature of IP laws will be one factor in the decision to make the investment, and where to locate.

Meet international undertakings and resolve disputes

Membership of the World Trade Organization and implementation of the TRIPS Agreement is a pragmatic reason for countries to have IP laws – for many developing countries, this factor has influenced major changes to their IP systems in recent years. The 'Uruguay Round' was a series of multilateral trade negotiations under the auspices of the General Agreement on Tariffs and Trade (GATT) than ran from 1986 to 1994. This led to the signing of the WTO Agreement, which comprised a comprehensive package of agreements. These agreements covered a wide range of trade issues, including agriculture, trade in other goods, trade in services, and IP. They also established a common system for resolving trade disputes.

Membership of the WTO requires compliance with all the multilateral agreements under the WTO Agreement – it's therefore not possible to join the WTO in the hope of benefits in other areas of trade and to avoid the obligations imposed by TRIPS. The TRIPS Agreement establishes a common standard for national IP systems, with some areas of flexibility and diversity. It also ensures that when two countries have a dispute about IP matters, the issue is resolved by an international process, in a transparent way according to agreed rules, rather than by leverage based on unrelated trade interests. Including IP rules, in the form of TRIPS, into the general WTO dispute settlement system has had some unexpected consequences – for instance, when Ecuador was denied effective access to the European market for its bananas, it was able to seek retaliation by proposing that it withdraw protection for certain forms of European-owned IP.

Recognise inventorship and creativity

Many of the reasons discussed above for intellectual property laws are economic reasons. Intellectual property laws contribute to the development of national economies in various ways. For example, intellectual property laws encourage and reward innovation and development, can lead to benefits from international trade opportunities, and can assist with attracting foreign investment and technology transfer.

Another justification for intellectual property laws is non-economic. That is, creators and inventors have a right to not only protect the results of their intellectual endeavours, but also to be recognised as the creators, or inventors, as such. This is why on a patent application the name or names of the inventors are required, even though the patent itself is owned by someone else, such as a university or corporation.

The costs of IP protection

In considering the operation and potential benefits of the IP system, it is important to bear in mind that the intellectual property also attracts criticism on several counts. These include concerns that IP protection can:

- create unjustifiable monopolies in the interests of large multinational companies;
- block access to new technology for developing countries;
- inhibit the flow and use of valuable information;
- force up the price of essential goods, such as pharmaceuticals, and making them effectively unobtainable;
- privilege western-style commercial and technological practices over those of other cultures and regions;
- set individual private rights over collective or community interests; and
- overrule ethical and environmental concerns.

On the other hand, others take the position that such criticisms overlook the positive possibilities of the IP system, fail to take account of the existing checks and balances available, or misrepresent the actual nature of IP rights. It is true that IPRs are rarely absolute or unlimited, and mechanisms for dealing with their abuse do exist. For example, the TRIPS Agreement recognizes:

- the need to 'ensure that measures and procedures to enforce IPRs do not themselves become barriers to legitimate trade;'
- the potential need for measures 'to prevent the abuse of IPRs by right holders or the resort to practices which unreasonably restrain trade or adversely affect the international transfer of technology;' and
- that some licensing practices or conditions pertaining to IPRs which restrain competition may have adverse effects on trade and may impede the transfer and dissemination of technology

The debate over these issues is diverse and wide-ranging, well beyond the scope of this handbook. However, a common theme is the need for balance, transparency and mutual benefit, so that the IP system serves the broader public interest as well as providing sufficient private incentives for beneficial development and transfer of technology, fair commercial practices and creative endeavour. How to strike this balance is both a question of public policy settings, and a matter for skilled, effective use and administration of the IP system.

1.6 What is the International Framework for Intellectual Property?

IPRs are integral to international trade, and the way they are protected can also arise as an issue in international trade disputes. Administration of IP systems is also very difficult to manage without international cooperation.

It is important that there is a harmonised system of IP laws to facilitate international trade in this important and growing part of the economy. The international framework for IP rights plays a major role in harmonising the protection of these rights throughout the world. The administration of international IP issues is conducted largely by the World Intellectual Property Organisation (WIPO). The WTO (especially through the TRIPS Council) also plays an increasingly important role in such matters.

Several international agreements on IP rights, including the TRIPS Agreement and the UPOV Convention, have already been referred to above. The key set of international treaties for the IP protection of biotechnology inventions are the:

- Paris Convention for the Protection of Industrial Property (1883);
- Patent Cooperation Treaty (PCT) (1970);
- Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure (the Budapest Treaty) (1977);
- Strasbourg Agreement Concerning the International Patent Classification (IPC) (1971);
- International Convention for the Protection of New Varieties of Plants (UPOV) (1961); and
- Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) (1994).

Other international agreements that have IP implications for biotechnology include:

- the Convention on Biological Diversity (1992); and
- the Food and Agriculture Organisation (FAO) International Treaty on Plant Genetic Resources (adopted 2001).

Other important international treaties concerning other aspects of IP include the:

- Berne Convention for the Protection of Literary and Artistic Works (1886) (copyright, including software); and
- WIPO Copyright Convention (1996) (updating copyright rules for the digital environment).

WIPO and the WTO

The World Intellectual Property Organisation (WIPO) and the World Trade Organisation (WTO) are the two main international bodies that administer and oversee international intellectual property obligations.

WIPO is a specialised agency of the United Nations and is based in Geneva. WIPO administers most IP treaties, including the Paris Convention, the PCT, the Budapest Treaty, and the Strasbourg Agreement on the IPC. WIPO also provides wide-ranging technical assistance to Developing Countries through its development cooperation program.

The multilateral trade negotiations of the Uruguay Round, within the framework of the General Agreement on Tariffs and Trade (GATT), led to the signing of the WTO Agreement in Marrakesh in 1994. This agreement provided for the establishment of the WTO, which commenced operation in 1995. Among the bundle of integrated trade agreements administered by the WTO is the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), a specific agreement setting standards for national IP systems and providing for dispute settlement on IP issues. The WTO is an international organisation entirely distinct

from WIPO, although both organisations are based in Geneva. WIPO and the WTO have a cooperation agreement to manage their overlapping responsibilities for international IP.

Paris Convention for the Protection of Industrial Property

The Paris Convention (1883) was the first multilateral agreement for industrial property including patents, trademarks and designs. It provides that each country must grant the same industrial property protection to nationals of other parties to the convention as it grants to its own nationals - the principle of 'national treatment.' The Paris Convention also provides rules in relation to the right of priority for applicants who file first in a Member's country – this means that if you apply for a patent in your own country first, you can still apply in other countries within 12 months and the effective date of the foreign applications will be the same as your original application. This has enormous practical consequences for those working with patents. (A similar right applies to trade marks and industrial designs, although the period is only 6 months.) Among other things, the Paris Convention also provides that patents granted in different countries are independent of each other – in other words, if a patent is cancelled in one country, it is not automatically considered invalid anywhere else; and acceptance in one country doesn't create an obligation to accept it anywhere else.

The Paris Convention does not provide detailed rules about the legal tests that a patent must satisfy to be eligible for patent protection. Indeed none of the international agreements provide detailed rules about the substantive legal tests that a patent must satisfy – this is the province of legislatures, patent administration and courts at the national level.

Patent Cooperation Treaty (PCT)

Patents are still protected country-by-country (there are several regional systems, one covering most European countries, one covering Eurasian countries, and two operating in Africa). This means that getting patent rights in a number of countries can be highly expensive and administratively difficult. This is especially a problem for small and medium enterprises with limited resources. The PCT (1970) was developed to create a streamlined mechanism for applying for patent protection in many countries at the same time – it does not replace the national level, but it does reduce the initial administration and cost, and reduces the uncertainty about the benefit of proceeding with further investment. In essence, it allows the applicant to buy time while maintaining their entitlement to gain patent protection at a national level, so that they can assess the viability of the invention, get commercial backing, and check the likely success of the patent application. The key benefits of the PCT system are:

- It is possible to comply with a number of formalities in a centralized manner, rather than initiating the detailed paperwork needed for patent applications in many countries. This can significantly reduce the costs of applications.
- It allows you to maintain a legally recognized priority date and provides time to assess the feasibility of your patent before paying for expensive national patent applications in many countries. As previously noted, establishing your priority date is important in the patent process because it establishes the date from which novelty is determined and the date from which your right can be recognised if you are granted a patent.
- It provides for an international search. The results of this search are very valuable to the applicant. They allow the applicant to make more informed choices early in the patent process, and to amend the application to deal with any conflicting material, before the major expenses of the national phase of the patent process begin. The PCT system also provides for an optional international preliminary examination. As discussed in *Module Two* and *Module Three*, this examination does not have any direct legal effect, but gives the applicant a useful practical indication of potential difficulties that might be encountered at

the national level, so that suitable action (e.g. amendment, or withdrawal) can be taken when it is still relatively inexpensive to do so.

There is no such thing as a 'world patent'. The PCT process is perhaps the nearest thing there is to a global patent, but it does not result in anything but a modified form of patent application at the national level, and requires you to interact with the patent authorities responsible for any country where you want patent protection. The PCT simply provides a streamlined process for the patent application process in many countries at the same time. After the PCT international phase, applicants must comply with the patent laws in each of the countries in which patent protection is sought. The patent process is described in *Module Three: Reading a Biotechnology Patent and the Patent Process*.

Budapest Treaty - Deposit of Microorganisms

Patent law requires that details of an invention must be disclosed in a patent specification. The new technology must be described sufficiently to allow others in the community to put the technology into effect, for research and other purposes initially, and without constraint once the patent term expires. However, when an invention involves a micro-organism these two requirements are difficult to satisfy. First, it is very difficult for the patent applicant to describe in writing inventions relating to food and pharmaceutical products that involve after the patent term is finished it is very difficult for a person in the community to work an invention that refers to a microorganism unless they actually have access to it.

To overcome these kinds of problems, the *Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure* (the Budapest Treaty) (1977) provides an easier way for patent applicants to satisfy the requirement for full description of biotechnology patents. The Budapest Treaty does this by providing for the deposit of a microorganism at a recognised "international depositary authority".

This procedure benefits patent applicants by saving them money. Members of the Budapest Treaty must recognise the deposit of a microorganism with any international depositary authority. This allows patent applicants to make one deposit with an international deposit authority rather than having to arrange deposits in each country in which patent protection is sought. The Budapest Treaty also sets up a mechanism to facilitate appropriate access to deposits.

Please see *Module Two: Biotechnology and Intellectual Property* for more details about patent law requirements.

Strasbourg Agreement Concerning the International Patent Classification

The Strasbourg Agreement Concerning the International Patent Classification (1971) sets up the International Patent Classification (IPC). The purpose of the IPC is to classify technology in a uniform way to make it easier to search patent documents using the IPC system of classification.

The IPC is used by patent offices in more than 80 countries and the secretariat of WIPO, which administers the PCT. According to WIPO, over the last 10 years IPC symbols have been put on over 1 000 000 patent documents.

A key part of the patent process is the searching of published documents to find out if an invention satisfies the legal tests for patenting such as novelty and inventive step. The search of published patent documents as part of the patent process is called a "prior art" search. Prior art, which includes search for novelty, is determined in accordance with prior publication in the field of technology that the claimed invention is for. Without a uniform system to classify patentable technology, such as that established by the IPC, searching for prior patent documents would be complex and unreliable.

The legal requirements for a patent are discussed in more detail in *Module Two: Biotechnology and Intellectual Property* and the practicalities of the IPC classification system are discussed in *Module Three* and *Module Four*.

International Convention for the Protection of New Varieties of Plants (UPOV)

The International Union for the Protection of New Plant Varieties (the UPOV Union) was established by the UPOV Convention, which was signed in 1961 and has since been revised three times. The acronym "UPOV" is from the French name of the organisation, which is *Union internationale pour la Protection des Obtentions Vegetales*.

The UPOV Convention sets out standards for national systems establishing rights for plant breeders who develop new plant varieties. For more information about plant breeders' rights see *Module Seven: Plant Breeders' Rights*.

UPOV provides for certain exclusionary plant breeders' rights over the propagating material of a protected variety. These rights include rights over the production, reproduction, sale, export and import of propagating material for protected plant varieties. UPOV also provides for exceptions for acts done for non-commercial purposes, experimental purposes and acts done for the purpose of breeding other varieties, and optionally for farmers to save seed for their future plantings.

A new plant variety must be distinct, uniform and stable in order to be granted plant breeders' rights.

The UPOV Union is supported by the Office of UPOV, which is headed by a Secretary-General. By agreement with WIPO, the Director General of WIPO is also the Secretary-General of the UPOV Union and UPOV is housed in the WIPO building in Geneva, although UPOV is a completely separate international organisation from WIPO, and has a separate secretariat. UPOV and WIPO work cooperatively together and UPOV shares its headquarters with WIPO in Geneva.

The only other international agreement that touches on plant breeder's rights is the TRIPS Agreement. It provides only very general obligations in relation to the protection of plant varieties – it calls for use either of the patent system, or an effective separate (or *sui generis*) system, or both, to protect new plant varieties. The standards in the UPOV Convention are a widely recognized instanceof this kind of *sui generis* system.

Agreement on Trade-Related Aspects of Intellectual Property Rights

The TRIPS Agreement is one of the major international IP treaties and is the only comprehensive international IP treaty. As noted above, TRIPS was one of the outcomes of the Uruguay Round of the GATT. It came into force on 1 January 1995. The TRIPS Agreement establishes the TRIPS Council, consisting of all WTO members, and is responsible for the administration of the TRIPS Agreement.

TRIPS builds on the existing IP standards in the WIPO Berne Convention for the Protection of Literary and Artistic Works (1886) and the Paris Convention (1883), and establishes international standards in the following areas of intellectual property.

Types of intellectual property covered by the TRIPS Agreement

- copyright and related rights
- trade marks
- geographical indications
- industrial designs
- patents
- layout designs of integrated circuits
- protection of undisclosed information
- new plant varieties

TRIPS also provides for remedies against anti-competitive abuse of each of these IP rights, such as coercive licensing practices.

The TRIPS Agreement is different from the WIPO treaties in two key ways. First, the TRIPS Agreement has detailed requirements for enforcement mechanisms in national legal systems (TRIPS Articles 41-61). Secondly, the WTO's Dispute Settlement Understanding provides an improved system for settling IP-related disputes between WTO Members. TRIPS was established to promote balanced systems for protecting the rights of creators and inventors, and to provide a more predictable, transparent and rules-based system that was available before to deal with international disputes over IP protection

Convention on Biological Diversity

The Convention on Biological Diversity (CBD) is an environmental treaty, which was opened for signature at the United Nations Conference on Environment and Development (the Rio Earth Summit) in 1992. The objectives of the CBD are the conservation of biological diversity, the sustainable use of its components, and the fair and equitable sharing of the benefits arising from the use of genetic resources.

Although the CBD is an environmental treaty it is relevant to a consideration of IP issues. The CBD recognises that patents and IP rights may have an impact on the objectives of the CBD and calls on parties to cooperate to ensure that IP rights are "supportive of and do not run counter to its objectives". Further, the CBD requires that each contracting party

> *Subject to its national legislation, respect, preserve and maintain knowledge, innovations and practices of indigenous and local communities embodying traditional lifestyles relevant for the conservation and sustainable use of biological diversity and promote their wider application with the approval and involvement of the holders of such knowledge, innovations and practices and encourage the equitable sharing of the benefits arising from the utilization of such knowledge, innovations and practices;*

This requirement has raised a number of issues concerning the protection of traditional knowledge and relationship between the CBD and TRIPS. Work is being done under the CBD to identify the ways in which IP rights impact on the objectives of the CBD. *Further Reading* pages and the *Annotated Bibliography* provides links to internet articles and websites where further research on this area can be done.

Treaty on Plant Genetic Resources for Food and Agriculture

The United Nations Food and Agriculture Organisation (FAO) recently concluded a treaty on plant genetic resources for food and agriculture, which has major significance for agricultural biotechnology, and the role of IP. It establishes a system of facilitated access to plant genetic resources that are held in public collections, with the aim of ensuring conservation and sustainable use of plant genetic resources for food and agriculture and the fair and equitable sharing of the benefits arising out of their use, in harmony with the CBD, for sustainable agriculture and food security.

Negotiations on the treaty highlighted issues concerning the balancing of the rights of IPR holders and the need for continued access to genetic resources and accessibility to protected varieties for food security. These raise issues of management and regulated use of IP rights, and the role of IP rights in relation to sharing the benefits from access to plant genetic resources for food and agriculture.

Biotechnology, Access to Genetic Resources & Traditional Knowledge

The CBD and FAO Undertaking mentioned above are just two elements of a broader international debate about the relationship between IP protection for biotechnology and such related matters as:

- ownership and control of genetic resources (such as plants and micro-organisms);
- recognition of traditional knowledge relating to plants and ecological systems (such as valuable knowledge about the healing qualities of plant extracts);
- incentives and benefits for conserving biological diversity (such as mechanisms for ensuring that local and Indigenous communities derive benefits from preserving the natural environment);
- prior informed consent for access to biological resources (such as legal requirements and mechanisms for ensuring that custodians or owners are properly involved and informed, and confirm their consent, prior to access to plant resources and related traditional knowledge in a protected area);
- equitable sharing of the benefits from research based on genetic resources and on related traditional knowledge (such as financial payments and royalties based on the commercialisation of products); and
- ethical and culturally based concerns about plant, animal and human biology (such as concerns that patent rights can in some cases cover life forms or life-processes).

This has led to claims, for example, that the CBD and the TRIPS Agreement are in conflict or tension because the CBD encourages collective ownership and management of genetic resources, while TRIPS provides for private rights (such as patent and plant variety rights) over innovations based on those resources. Others suggest that these two mechanisms can work effectively together, for instance if the patent system can be used to generate benefits that are shared with the custodians of genetic resources in exchange for access to those resources, for instance by creating contractual agreements. These are complex and contentious issues, and the various modules in this training package may provide insights into how they can be addressed.

Another international issue has been the interaction between IP rights and farmers' rights. In 1989, a resolution by the FAO defined 'farmers' rights' as 'rights arising from the past, present and future contributions of farmers in conserving, improving and making available plant genetic resources, particularly those in the centers of origin/diversity.'

Regional Agreements on Intellectual Property

In addition to the international intellectual property agreements discussed above, there are several regional agreements on IP that are particularly relevant to countries in the Asia-Pacific region. For example:

- the Association of South-East Asian Nations (ASEAN) has a Framework Agreement on IP, and

- the Asia-Pacific Economic Cooperation (APEC) has an Intellectual Property Rights Experts Group (IPEG) that promotes intellectual property rights.

APEC IPEG initiatives

The APEC IPEG provides practical support for APEC-wide implementation of TRIPS. It promotes a more efficient and harmonised administration and enforcement of intellectual property rights backed by greater public awareness and more skilled use of the intellectual property system in the business and public sectors. IPEG also promotes policy dialogue and exchanges of information on emerging issues.

APEC-IPEG members comprise Australia, Brunei Darussalam, Canada, Chile, Chinese Taipei, Hong Kong, China, Indonesia, Japan, Republic of Korea, Malaysia, Mexico, New Zealand, Papua New Guinea, People's Republic of China, Peru, Republic of the Philippines, Russia, Singapore, Thailand, United States and Vietnam.

ASEAN Framework Agreement

The ASEAN Framework Agreement on intellectual property promotes wide-ranging intellectual property objectives. It promotes:

- the strengthening of civil and administrative procedures and remedies for infringement of intellectual property rights
- the provision of technical cooperation for the implementation of TRIPS in relation to patent search and examination, computerisation and human resources development;
- compliance of TRIPS-consistent intellectual property laws;
- the implementation of an ASEAN Regional Trademark and Patent Filing System;
- the implementation of an ASEAN Common form for Trade Mark and Patent applications; and
- the public awareness of intellectual property in the public and private sectors.

ASEAN members comprise Brunei Darussalam, Cambodia, Indonesia, Laos, Malaysia, Myanmar, the Philippines, Singapore, Thailand and Vietnam.

1.7 Summary - Module One

What is intellectual property?

Intellectual property is a system of limited legal rights granted to reward inventive and creative endeavours, and to limit commercial free-riding. Some types of intellectual property rights relevant to biotechnology are:

- patents for new inventions
- plant breeders' rights for new plant varieties
- protection for new industrial designs
- trade secrets for technical business or commercial information
- trade marks for distinguishing marks of products or services.

Why do we have intellectual property rights?

Intellectual property rights can benefit individual researchers, industry, national economies and the community. Some objectives for the grant of intellectual property rights are to:

- reward inventors for their inventive endeavours
- encourage research and innovation for the benefit of the community
- assist inventors and industry to effectively commercialise their inventions and innovations
- assist the development of national economies by encouraging and rewarding innovation, and facilitating access to benefits from international trade opportunities
- attract foreign investment and technology transfer
- comply with international standards
- recognise an inventor's right to benefit from their invention.

What is the international framework for intellectual property rights?

The international framework for intellectual property rights and biotechnology includes:

- the WTO TRIPS Agreement, which covers patents, plant breeders' rights, trade secrets, trade marks, copyright, designs and integrated circuits, and enforcement and dispute settlement.
- the Paris Convention for the Protection of Industrial Property, which provides rules on patents, trade marks, designs and unfair competition
- the Patent Cooperation Treaty (PCT), which provides a streamlined process for making an international patent application with the effect or reserving rights in many countries at once
- the Budapest Treaty for the Deposit of Microorganisms, which provides an easy way for patent applicants to refer to a microorganism in the description of their invention
- the Strasbourg Agreement Concerning the International Patent Classification (IPC), which sets up the IPC system of technogical classifications, facilitating patent searching
- the International Convention for the Protection of New Varieties of Plants (UPOV), which provides international standards in relation to the protection of new varieties of plants
- other agreements that are primarily environmental but have implications for intellectual property such as the Convention on Biological Diversity (CBD) and the Food and Agriculture Organisation (FAO) International Treaty on Plant Genetic Resources.

1.8 Group exercises - Module One

Module One sets out an introduction to intellectual property law. Please discuss Module One with your fellow participants and prepare answers to the following questions. You could either use the questions as a basis for general discussion, or prepare individual answers to the questions.

Exercise 1.1 - comparison of different types of intellectual property

Please review the material in this Module on:

- Patents
- Trade secrets (confidential or undisclosed information)
- Plant breeders' rights
- Trade marks

and refer to the relevant sections in the TRIPS Agreement in *Annex One*. Prepare a comparative table based on the following format, and answer the questions for each IP right, writing down the relevant TRIPS Article(s) where appropriate.

	Patents	**Trade secrets confidential information**	**Plant breeders' rights**	**Trade marks**
What kind of material is eligible to be protected by this right?				
What kind of limitations, restrictions or exceptions to this right are available?				
What do you need to do to get this right?				
Is there a limited term of protection? If yes, what is it?				
Give practical examples of how this right could be (i) a useful benefit, or (ii) an impediment to a business or other enterprise in your country.				

Exercise 1.2 - different types of intellectual property can exist in one product

You and your university research colleagues have invented eye drops that soothe sore, itchy and red eyes affected by air pollution. You used a new production method to develop the eye drops. In doing so, you have created a new shape of dispenser which could also be used as a distinctive bottle for the eye drops – it looks strikingly new, but also functions in a new way that makes it easier to use for patients treating their own eyes. You have also found that adding a particular mixture of natural products to the eye drops improves their effect. You want to market your invention with the trade mark "Cee Clear" and a logo consisting of a stylised 'C and eye' design. You are also applying to receive the official certification of this product by the semi-government Eye Care Council in your country.

CeeClear

What kinds of intellectual property rights could you use for your product?

What sort of issues would you need to address in gaining those rights?

Who would own the rights – you and your colleagues, the university, or a separate company? What approach would be best:

- in ensuring the product was commercially successful?
- in ensuring that your university was able to fund future research?

Exercise 1.3 - Benefits of international intellectual property treaties

There are many international treaties that have contributed to a harmonized international framework for intellectual property protection – the TRIPS Agreement is one of many, and TRIPS is itself based on other treaties that were negotiated over many years. The harmonised intellectual property system includes common basic legal standards, similar administrative processes (or directly integrated administration), and common standards for such matters as classification and publication.

What are the potential benefits and the potential problems of an internationally harmonised IP system?

Exercise 1.4 - Benefits of intellectual property to your country

How can intellectual property rights benefit you and your country? What costs and potential disadvantages are there? TRIPS suggests that the IP system should

- contribute to the promotion of technological innovation and to the transfer and dissemination of technology,
- to the mutual advantage of producers and users of technological knowledge
- and in a manner conducive to social and economic welfare, and to a balance of rights and obligations.

How do you think these objectives for the IP system could best be achieved in your country? How can these objectives be achieved in the work of your own organisation or institution?

FOREIGN AFFAIRS AND TRADE

AusAID the Australian Government's overseas aid program

Module Two

Biotechnology and Intellectual Property

Intellectual Property and Biotechnology
A Training Handbook

Contents: Module Two

2.1 Objectives for Module Two

This Module aims to give an introduction to:

- examples of biotechnology inventions, including in the field of pharmaceutical products and agriculture
- the difference between inventions that can patented and inventions that cannot be patented
- the three key criteria that make an invention eligible for a patent right, that is, novelty, inventive step and industrial application
- the requirement of "full description" of biotechnology inventions in patent specifications
- how the Budapest Treaty on the deposit of microorganisms makes it easier for inventors to provide a full description of their invention when it involves a microorganism
- the requirement that claims in a patent application must be fairly based on the description of the invention in the application, and
- ethical and social aspects of biotechnology patents.

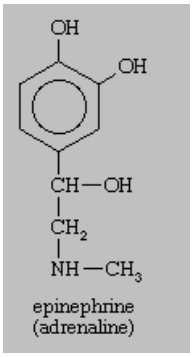
2.2 Background to Biotechnology

I cannot stop without calling attention to the extraordinary condition of the law which makes it possible for men without any knowledge of even the rudiments of chemistry to pass upon such questions as these. The inordinate expense of time is the least of the resulting evils...How long we shall continue to blunder along without the aid of unpartisan and authoritative scientific assistance in the administration of justice, no one knows; but all fair persons not conventionalized by provincial legal habits of mind ought, I should think, unite to effect some such advance.

This quotation, dating from 1911, occurs in an important US court judgement on a patent for the isolation of the natural hormone, adrenalin (or epinephrine). This technology would now be considered to be biotechnology, even though it was developed by a Japanese scientist at the turn of the last century, some forty years before the term 'biotechnology' was first recorded. It shows that how to reconcile biotechnology issues with the legal concepts of intellectual property is not a new problem. The kind of issues that are current today mirror concerns in the past.

What has made it especially important today, however, is the sense that recent biotechnology offers potentially enormous benefits for human well-being, nutrition, health and technological and industrial development, and the various perceptions that intellectual property can either greatly help or greatly hinder those benefits. In putting biotechnology to work for the general well-being, is intellectual property the problem or the solution? One important way of finding solutions is for a greater convergence of skills between the scientific and the legal – exactly as Judge Hand called for nearly a century ago.

Early developments in biotechnology



While biotechnology has developed rapidly in recent years, the main beneficial applications of biotechnology – for agriculture and for human health – have been identified for a long time. For example, the isolation of adrenalin over a century ago from the human suprarenal gland was an important advance. In 1901, the *American Journal of Physiology* reported that 'the most important contribution to our knowledge of the active principle of the suprarenal gland ... is from Dr. Jokichi Takamine who has isolated the blood-pressure-raising principle of the gland in a stable and pure crystalline form... To this body...he has given the name *Adrenalin.*'

The application of technology to agriculture has helped contribute to enormous increases in yield and quality of the produce. This has been through selective breeding and improved technologies for fertilisation and pest and weed management. At the dawn of the modern era of chemistry, in 1841, Friedrich List speculated on the future directions of 'agricultural chemistry:'

> The culture of the potato and of food-yielding plants, and the more recent improvements made in agriculture generally, have increased tenfold the productive powers of the human race for the creation of the means of subsistence. In the Middle Ages the yield of wheat of an acre of land in England was fourfold, to-day it is ten to twenty fold, and in addition to that five times more land is cultivated. In many European countries (the soil of which possesses the same natural fertility as that of England) the yield at present does not exceed fourfold. Who will venture to set further limits to the discoveries, inventions, and improvements of the human race? Agricultural chemistry is still in its infancy; who can tell that to-morrow, by means of a new invention or discovery, the produce of the soil may not be increased five or ten fold?

The food industry, too, has depended on technologies drawing on the life sciences. In their time, the identification and purification of particular strains of bacteria were important in the creation of new forms of cheese, in baking and production of beer, wine and other foodstuffs.

The famous Roquefort cheese (legally recognised in France since 1411) depends on the selection and cultivation of a particular microorganism, *penicillium*

roqueforti, used in the fermentation of the cheese. It originated in the village of Roquefort-sur-Soulzon in France, and is ripened in limestone caves in that area.

The intellectual property system has been used for many years to protect the interests of cheesemakers in the Roquefort district. Some aspects of the cheesemaking process used in the Roquefort district are protected as trade secrets. The Roquefort Société des Caves was established in 1842, a company formed by local producers, and it registered a distinctive oval trade mark in 1863. The French Government, in 1924, gave formal recognition to the term 'Roquefort' as a protected appellation of origin (a form of geographical indication).

Similar protection has been gained overseas. For example, the Community of Roquefort registered the word *Roquefort* as a certification trade mark for cheese in the United States in 1952, with the condition that:

> THE CERTIFICATION MARK IS USED UPON THE GOODS TO INDICATE THAT THE SAME HAS BEEN MANUFACTURED FROM SHEEP'S MILK ONLY, AND HAS BEEN CURED IN THE NATURAL CAVES OF THE COMMUNITY OF ROQUEFORT, DEPARTMENT OF AVEYRON, FRANCE.

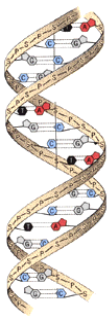
Protection of microorganisms and related processes by the patent system equally has a long history. In 1873, the French scientist Louis Pasteur received a US patent for a method of purifying yeast for use in making beer, for the yeast derived by that method, and for the apparatus used to purify the yeast, on the basis of the significant improvement to beermaking technology that was disclosed in the patent document.

What is biotechnology?

'Biotechnology' is a very broad term, with no specific meaning in intellectual property law in general. However, one important international definition is contained in the multilateral environmental agreement, the Convention on Biological Diversity, which defines 'biotechnology' as:

> any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use.

It relates to the applied forms of biological science, and generally speaking refers to the technological use of organisms and organic processes to produce outcomes which have economic or industrial value. Fermentation techniques and traditional plant cross breeding are examples of historically important forms of biotechnology (many of which remain highly important economically). In its broadest sense, biotechnology has been used by humankind since before recorded history, for example baking bread and brewing beverages, cheesemaking, and conventional breeding of plants and animals.



More recently, biotechnology has come to refer to the processes and products associated with manipulation of DNA, and the technologies resulting from gene sequencing. 'Biotechnology' includes the more specific term 'genetic engineering.' Genetic engineering itself has a broad sense, including modifying or manipulating organisms by controlling reproductive processes (for example, in vitro fertilization and artificial insemination), and a more recent, specific sense of recombinant DNA technology – the techniques of joining or recombining DNA material to create new genetic combinations which then can be propagated to produce a desired new outcome. It is also sometimes referred to as genetic modification, gene technology, or genetic manipulation.

In distinguishing the general background of biotechnology from these significant recent technologies, the Biosafety Protocol (The Cartagena Protocol on Biosafety to the Convention on Biological Diversity) defines 'modern biotechnology' as the application of:

> *in vitro nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or*
>
> *fusion of cells beyond the taxonomic family,*
>
> *that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection.*

The scope of recent biotechnology includes:

- genetics and genomics, genetic engineering, cloning;
- gene therapy, detection, replacement, tagging, sequencing and product analysis etc;
- proteomic, protein engineering, detection, sequencing, product analysis etc;
- enzyme technologies, replacement, analysis etc;
- molecular biology;
- cell and tissue culture;
- monoclonal antibodies;
- bio-sensors; and
- bioinformatics

Other more traditional applications of biotechnology (such as isolation, breeding, and selection) remain economically and technologically important – and still continue to attract intellectual property protection – but it is these 'modern' biotechnologies that have attracted the most attention in terms of their impact and relationship with the intellectual property system.

Applications of biotechnology

The applications of biotechnology are increasingly diverse: it may contribute to the manufacture or modification of existing products, create modified plants and animals with particular traits, or develop new strains of micro-organism with especial functions. Biotechnology can therefore create existing products in new, more efficient ways, produce new substances that cannot be created by conventional technologies, and create new processes. All these applications are potentially the subject of intellectual property claims.

A great deal of research and patenting activity has covered new genetic engineering methods such as the recombinant DNA technology, monoclonal antibody production and cloning, developed in the 1970's allowing the controlled addition or deletion of genetic material to or from organisms, and used for manufacture of diagnostics or therapeutics as well as many other applications.

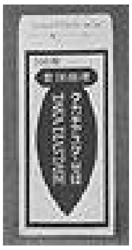
One report cites the following current and future applications of biotechnology:

- waste disposal through the action of micro-organisms;
- large-scale fermentation to produce specialty chemicals and pharmaceuticals;
- pharmaceuticals and other human therapeutics, including natural products;
- human diagnostic products;
- diagnostic services;
- cosmetics;

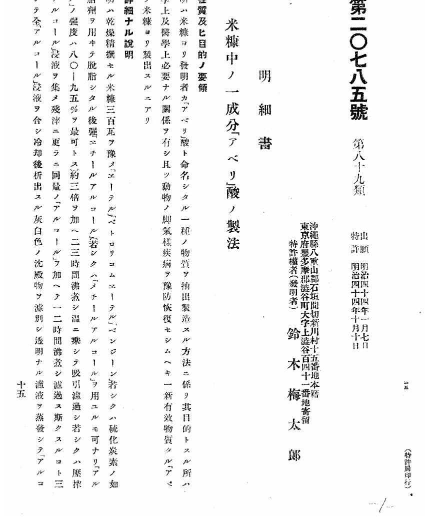
- animal breeding, veterinary medicines and diagnostics;
- agriculture, plant breeding;
- environmental management, pollution control and remediation, water treatment;
- minerals processing and leaching;
- food production and processing; and
- biomass for the production of fuels and energy.

Background to intellectual property and biotechnology

Just as biotechnology is not, in itself, a new technology, the interaction between intellectual property and biotechnology has been considerable. This has included patents on biotechnology products and processes. An early example was the US patent granted to Louis Pasteur on yeast used in brewing beer. But it has also included use of trade marks, geographical indications and trade secrets (as in the case of Roquefort cheese cited above).



Another early example of patents in the biotechnology sphere was the work of Jokichi Takamine, a biochemist who also served as Japanese Deputy Commissioner of Patents. He obtained a patent for the improved brewing methods using yeast which he developed in 1890. In 1894 he received a patent for Taka-Diastage, a form of the starch-digesting enzyme diastase produced by the pancreas, which he had isolated from the fungus Aspergillus oryzae, a fungus growing on rice. This technology was taken up, with his assistance, by the distilling industry in the United States. He was also the first to isolate a pure hormone from nature, namely adrenalin from the human suprarenal gland, greatly facilitating its clinical use. For this he also received a patent.


特許第二〇七八五號 第八十九類

出願 明治四十四年一月七日
特許 明治四十四年十月十日

沖繩縣八重山郡石垣間切新川村十五番地本籍
東京府豐多摩郡澁谷町大字上澁谷百四十一番地寄留
特許權者(發明者) 鈴木梅太郎

明細書

米糠中ノ一成分「アベリ」酸ノ製法

發明ノ性質及ヒ目的ノ要領

本發明ハ米糠ヨリ發明者カ「アベリ」酸ト命名シタル一種ノ物質ヲ抽出製造スル方法ニ係リ其目的トスル所ハ生理學上及醫學上必要ナル關係ヲ有シ且ツ動物ノ脚氣樣疾病ヲ豫防恢復セシムヘキ一新有效物質タル「アベリ」酸ヲ米糠ヨリ製出スルニアリ

發明ノ詳細ナル說明

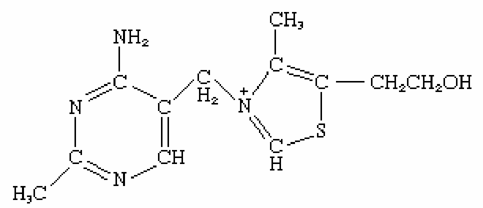
本發明ハ乾燥精撰セル米糠三百瓦ヲ豫メ「エーテル」「ベトロリコムエーテル」「ベンジーン」若シクハ硫化炭素ノ如キ脫脂劑ヲ用キテ脫脂シタル後強「エチールアルコール」若シクハ「メチールアルコール」ヲ用ユルモ可ナリ「アルコール」ノ強度ハ八〇—九五％ヲ最可トス約三倍ヲ加ヘ二三時間沸煮シ温ニ乘シテ吸引濾過シ若シクハ壓搾シテ「アルコール」浸液ヲ集メ殘滓ニ更ラニ同量ノ「アルコール」ヲ加ヘテ一二時間沸煮シ濾過ス斯クスルコト三回ニシテ全「アルコール」浸液ヲ合シ冷却後析出スル灰白色ノ沈澱物ヲ濾別シ透明ナル濾液ヲ蒸發シテ「アルコ

十五

一五

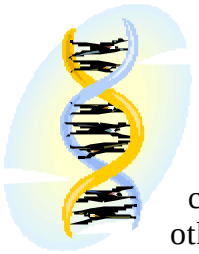
(特許局印行)

Faced with a major health crisis in the early years of the 20th century, the Japanese government established a special commission into the disease beriberi, which was then a major cause of death in Japan and in other Asian countries. Ultimately it transpired that this was due to the preponderance in the diet of polished white rice. Dr. Umetaro Suzuki's research led to his discovery that a substance in rice bran (then known as *aberic acid*, later called *thiamin* or Vitamin B1) prevented the disease, and he isolated this compound from rice bran, the first vitamin to be isolated. In 1911, he received Japanese patent 20785 in 1911 for this breakthrough (its first page is illustrated here).



In 1908, Professor Kikunae Ikeda identified the source of the flavor of kelp, a common ingredient in Japanese food, as glutamic acid (monosodium glutamate or MSG), which is naturally present at high levels in kelp, tomatoes and Parmesan cheese. Professor Ikeda discovered that soup stocks made from kelp contained high levels of this substance, a discovery forming the foundation of a major industry producing MSG from seaweed. It was introduced onto the market the following year under the brand *AJI-NO-MOTO*. MSG was used widely as a flavour enhancer, and was also used to treat hepatic coma. This formed the basis of a major industry, and Ajinomoto Co., Inc. is a large, diversified food business with international operations and sales of *AJI-NO-MOTO* in over 100 countries, with 15 factories still supplying one-third of the world's MSG market of some 1.5 million tons.

Modern biotechnology and intellectual property



The decoding of the double helix structure of DNA (deoxyribonucleic acid) by Frances Crick and James Watson in 1953 was a major scientific breakthrough that helped usher in the new technology of modern biotechnology, by setting the scene for an understanding of the precise method for reproducing specific inherited characteristics. A DNA molecule consists of two long chains of sugar and phosphate groups, twisted around each other in a double helix or spiral; each sugar group is attached to a base (which can be one of Adenine, Cytosine, Guanine or Thyamine, usually denoted by their first letters, A, C, G and T). Each sugar-phosphate-base compound is known as a nucleotide. The order of these groups with an A, C, G or T base within a strand of DNA provides the information required for cells to reproduce, and is thus the basis for genetic inheritance in all organisms - the 'genetic code.' A gene is a unit of inherited material, which is contained in a particular sequence of DNA. Long DNA chains are coiled and folded into compact structures known as chromosomes. The code on the DNA equally provides the information necessary for the creation within each cell of the many proteins that are required for organisms to function.

As the functioning of the DNA became better known, subsequent discoveries made possible a major new field of genetic engineering, involving the alteration of DNA in a living cell, by identifying a gene with useful properties, cloning it (growing a copy of it) and inserting it into a host. To clone a gene it is inserted into vector DNA, usually a bacterial plasmid (these are small, mobile rings of DNA, that are found in self-replicating bacteria, and confer biological traits such as antibiotic resistance and the ability to produce toxins). One of the most significant modern advances in biotechnology was the collaboration of Herbert Boyer and Stanley Cohen in the 1970s that created gene-splicing technology. This stemmed from their meeting at a scientific seminar on bacterial plasmids, when they found that their research paths converged in an interesting way.

The Cohen Boyer patents

Cohen had succeeded in introducing into the *Escherichia coli* (E. coli) bacterium the plasmid known as *pSC*101, which conferred resistance to the antibiotic tetracycline. He isolated specific antibiotic-resistant genes on the plasmids, and cloned them individually. Boyer's work had focussed on identifying how cells locate the necessary DNA sequence within a long strand of DNA to produce a specific protein. This led to the discovery that a particular enzyme, known as a restriction enzyme, produced by bacteria to defend against certain viral organisms (bacteriophages), could sever the DNA strand where the necessary sequence was located – this produced DNA segments with 'cohesive ends' that would adhere to other DNA fragments.

From discussions of their different research findings, the two scientists considered that the two technologies could be combined – combining Cohen's plasmid, used as a vehicle or 'vector' for carrying DNA segments, with Boyer's restriction enzyme, thus creating a mechanism for reproducing or cloning specific, individual DNA segments. In their joint research, they found that the enzyme *Eco* RI could cut the ring plasmid at a single location. Where the DNA was cut, they inserted a gene that conferred resistance to another antibiotic, kanamycin. When the E coli bacteria containing this modified plasmid then reproduced, their descendants were also resistance to both tetracycline and kanamycin. Broadening their approach to other species, they also succeeded in introducing genes from a toad into the bacteria, which then reproduced the same genes.

This insight and the experimental work was a key contribution to the creation of modern recombinant DNA technology: the technology that allows for new forms of genetically engineered DNA to be created by splitting DNA molecules and joining together specific DNA

fragments. This had enormous implications for medicine and the development of new pharmaceuticals, but also more generally for industry and agriculture.

The key aspects of this advance were:

- The use of living organisms to carry genes from one organism to another;
- The use of enzymes to cut and reattach the fragments of DNA that contain genes; and
- The capacity to target specific elements of DNA molecules from one organism, and to insert these isolated fragments directly into the DNA of another organism

In short, the capacity to identify and isolate specific DNA fragments (which could constitute a particular gene) was coupled with the capacity to introduce these fragments into the DNA of another cell, thus transferring that gene's property to the new cell, to be automatically reproduced when that cell subsequently reproduces through its normal biological processes.

In a pattern that is familiar, the scientists focussed on the science of their groundbreaking work, and did not consider patenting issues. However, a report of their work in the New York Times came to the attention of the technology licensing office of one of their universities, Stanford. Even though elements of the invention had already been published, owing to a 'grace period' provision in US patent law, there was still a limited time in which they could file for a patent. The application was lodged in 1974, and resulted (in amended form) in three US patents. The first one to be issued was US patent 4237224: process for producing biologically functional molecular chimeras (a copy of this document is provided in Module Three). This patent has already been referenced by 220 subsequent US patents, demonstrating how the disclosure in this patent document has been built on to produce numerous further technical advances. Later, related patents were 4468464 and 4740470 which related to biologically functional molecular chimeras.

Example: a biotechnology patent claim

The main claim of US patent 4237224 granted to the Cohen-Boyer invention of gene splicing is directed to:

A method for replicating a biologically functional DNA, which comprises:

- transforming under transforming conditions compatible unicellular organisms with biologically functional DNA to form transformants; said biologically functional DNA prepared in vitro by the method of:
  (a) cleaving a viral or circular plasmid DNA compatible with said unicellular organism to provide a first linear segment having an intact replicon and termini of a predetermined character;
  (b) combining said first linear segment with a second linear DNA segment, having at least one intact gene and foreign to said unicellular organism and having termini ligatable to said termini of said first linear segment, wherein at least one of said first and second linear DNA segments has a gene for a phenotypical trait, under joining conditions where the termini of said first and second segments join to provide a functional DNA capable of replication and transcription in said unicellular organism;
- growing said unicellular organisms under appropriate nutrient conditions; and
- isolating said transformants from parent unicellular organisms by means of said phenotypical trait imparted by said biologically functional DNA.

By mid-1995, reportedly 350 licenses had been granted for this patented technology, and in 1995 this produced royalties of about $27 million for the scientists' two universities, Stanford and the University of California. The licensing of this patent is further discussed in *Module Nine: Licensing and Enforcing Intellectual Property Rights*. With the involvement of Robert Swanson, a venture capitalist, this technology also led to the creation of one of the first biotech companies, Genentech, in 1976. This company produced the first human protein in a microorganism (somatostatin in the E coli bacterium), and in 1978 cloned human insulin, followed in 1979 by cloned human growth hormone. This led to the release of the first genetically engineered drug, human insulin, in 1982. This was licensed to the pharmaceutical company Eli Lilly, which marketed it under the trade mark Humulin. In 1985, Genentech released a further product, Protropin, a human growth hormone for treating children with growth hormone deficiency. Genetech currently holds over 650 US patents.

From the laboratory to the clinic: cloned human insulin

The mass production of cloned human insulin has been a major benefit for many people who suffer from diabetes. In the past, to manage their condition, they relied on injections of insulin derived from pigs and cattle, but this was expensive, difficult to obtain, and not identical to human insulin. The ready production of human insulin has resulted from advances in genetic engineering that stemmed from Cohen and Boyer's development of gene splicing technology.

Once scientists identified the human gene for making insulin, this could be cloned using recombinant DNA techniques so that human insulin could be produced by the bacterium *Escherichia coli*, a production process that could yield large amounts of insulin relatively cheaply. This proved a significant breakthrough for treating diabetes.

This product was developed by the pioneering company Genentech. The cloned human insulin was approved for therapeutic use by the US Food and Drug Administration. Genentech, lacking the commercial capacity to market a new pharmaceutical, licensed the technology to the major pharmaceutical company Eli Lilly, which sold it under the registered trade mark Humulin. Humulin was registered in 1981 as US trade mark 1201754 in respect of 'insulin' by Eli Lilly and Company. A further registration, number 2345798, of this trade mark in 2000 extended this coverage to pre-filled insulin delivery device. This trade mark has been registered elsewhere – for instance, in Australia, 'humulin' is registered in respect of 'pharmaceutical preparations and substances' (trade mark 649057) and 'medical apparatus including a pre-filled insulin delivery device' (trade mark 812212). Even when the original patents expire, and other producers can make use of the same technology, the recognition that has built up of the trademark over years can lead to a continuing marketing advantage.

This case demonstrates that bringing a new biotechnology product to market involves much more than just doing the basic research, or gaining a patent for an invention. In this case, it involved:

- creating a suitable enterprise for undertaking applied research, Genentech, backed by venture capital
- obtaining separate regulatory approval for release of the new product (in this case, through the US Food and Drug Administration, and similar authorities in other countries), often involving considerable additional expense for clinical trials
- licensing deal with a major pharmaceutical company for the production, marketing and distribution of the product

- related intellectual property, such as a distinctive registered trade mark, which can remain in force long after the patent for the underlying technology has expired, and can be extended to related products (such as insulin delivery devices in this case)

This provides a brief introduction to these considerations which are covered in more detail in *Module 10: Case Studies on Commercialising Research*

There are many applications for biotechnology using gene technology in the agriculture, pharmaceutical, textile and other industries. For example, genetic engineering in agriculture has led to the development of plants that are tolerant to herbicides and resistant to pests and diseases, in turn decreasing costs of farming as the yield of crops is increased and the cost of using herbicides is decreased. Biotechnology techniques have also led to the making of genetically engineered plants that produce better quality crops that produce an increased yield, and to the development of new and better drugs for the treatment of disease.

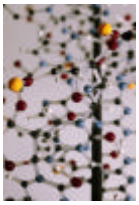
It can take many years of expensive research to develop new pharmaceuticals, agricultural products or genetically modified organisms. Therefore, it is important for scientists, biotechnology companies and research institutions to know how to protect their investment, particularly through the use of patents.

The use of biotechnology to create genetically modified organisms also raises controversial policy issues especially relating to the social and ethical aspects of biotechnology. It has raised the debate about whether, or how, the patent system should be used to regulate the ethical aspects of biotechnology. These issues arise, for instance, later in this module in relation to particular cases considered by the European Patent Office.

2.3 Overview of patenting principles

Not every technological advance, idea, scientific breakthrough or insight is eligible for a patent right, and the application of patent rules is different in differing countries. But there are some basic principles that apply almost universally. These may be expressed as a series of questions. Here we apply these questions in considering whether a patent might be granted for an imaginary new process or product which we will call 'Project Lambda.' To be eligible for a patent, Project Lambda will have to pass each of these tests.

Does Lambda fall within the definition of an 'invention'?



Crick and Watson's determination of the structure of the DNA molecule was a major scientific discovery, meriting a Nobel prize. But for all its valuable insight, determining the structure of the DNA molecule would not generally be considered an invention in patent law. If Lambda were a formula or a newly discovered law of nature (for example, concerning gravity waves or the ring structure of benzene) then it could not be patented.

Is Lambda forbidden subject matter for a patent?

Even if it falls within the definition of an 'invention,' the material might fall within a forbidden category. For example, your country might have a rule that prohibits patents on inventions that would be dangerous to human health or the environment, or contrary to morality or social order, if they were exploited; it could exclude patents on human beings. So a method for cloning human beings could be, in theory, an 'invention' but still be refused patent protection,

on the basis that it is considered contrary to public morals, or because it is specifically excluded patentable subject matter.

The European Patent Office recently clarified that it had issued a patent (EP 0695351) in error, because one of its claims referred to 'a method of preparing a transgenic animal' when this should have said 'a method of preparing a non-human transgenic animal' precisely because of such a prohibition. The underlying invention may have been equally inventive, technically, whether or not it was applied to humans or non-humans, but because of ethical concerns it could not be patented in relation to human beings.

Other prohibitions in effect in some countries include methods of medical treatment, and biological processes for producing plants and animals. Some examples of these are given in Module One.

If Lambda concerned a method of human cloning, a method for producing a genetically altered human being, or a new microorganism for use in war to destroy an enemy's staple food crops, even if it were a significant invention in technical terms, it would very probably be considered unsuitable subject matter for a patent.

In a famous case, Chakrabarty, the US Patent Office had rejected a claim to a new bacterium on the basis that 'as living things, microbes are not patentable subject matter' – in other words, even though the bacterium otherwise fitted the criteria to be patented, it fell into the category of prohibited subject matter. The US Supreme Court reversed this decision, determining that whether or not a material was a living thing did not in itself rule out an entitlement for a patent: the new microorganism was 'not nature's handiwork, but his own,' i.e. a human invention. The Court looked back at the legislative record, and found that when the patent law was passed by US Congress, it was the intention that patents be available to 'anything under the sun made by man' (see the box below on 'microorganisms as patentable subject matter.'

Is Lambda 'new' or 'novel'?

The claimed invention, at the effective date of the patent application, must be a genuine contribution to public knowledge. An invention can fail to meet this test in various ways – either someone else came up with the idea earlier, and somehow published, exploited or demonstrated it; or the inventors themselves publish the idea before applying for a patent.

Lambda is considered not novel or new if the same invention was already available to the public at the time you applied for a patent, for example in an earlier published document or in another public context. For example, Project Lambda might be a new method for desalination of water. You could have devised this independently, with extensive research and inventive work. But if someone else had separately came up with the same idea, and published it or used it in public before your patent application, then you would generally not be able to gain a patent because your invention would not be new or novel. Similarly, if you had already disclosed your invention to a potential investor or to a seminar on desalination technology, you would not normally be able to obtain a valid patent, because your invention was already known to the public when you applied for the patent.

Is Lambda 'non-obvious' or 'inventive'?

It isn't enough for Lambda to be new – there has to be an element of inventiveness, an 'inventive step', for it to be eligible for a patent. Say, for example, that you are researching into methods of treating a skin disease that affects horses. You come across a patent document that describes a method for treating the same disease, or a very similar disease, in cattle; but there is no evidence that this method has ever been used or applied to horses. You do some

clinical trials and find that the method (with some trivial adjustments, drawing on your general expertise in the area) is just as effective for treating horses. This finding is new or novel, in the sense that it has never been published or carried out before. But it would probably be considered an obvious extension of the existing knowledge contained in the patent about treating cattle, and thus not eligible for a patent in itself – for anyone working in the field, it would be obvious to try this method to treat horses (even if no-one had ever got around to doing it). The situation might be different if you had to overcome considerable hurdles in finding a way of applying the method to horses, because of their different physiology or because the disease affected them in a different way.

For example, a pharmaceutical company patented an entirely new set of chemical compounds that were derived from guanadine (an alkaline crystalline compound formed by the oxidation of guanine, a product of protein metabolism found in urine). These were patented on the basis of utility in treating high blood pressure in mammals. Subsequently, it was found that these compounds were also useful in treating diarrhoea in mammals and poultry, and this was sufficiently non-obvious for this second use of the same compound to be granted a separate patent.

Is Lambda 'useful' or 'capable of industrial application'?

Patents are intended to cover applied technological knowledge, and they are intended to give rights on the basis that they provide a genuinely useful solution to a practical problem. This means that the invention cannot be an abstract idea or a general observation. This requirement often overlaps with the basic definition of 'invention.' In one Australian court case, the nature of a patentable invention was described as 'a mode or manner of achieving an end result which is an artificially created state of affairs of utility in a field of economic endeavour.' Generally, a patented invention should have some practical value and application. It should also be useful in the sense of not contravening the laws of nature – you cannot patent a process that generates energy in violation of the laws of thermodynamics.

This requirement also means that the invention should be able to achieve the practical outcome claimed for it. For example, say you were doing research into a new class of chemical compounds, and you speculated that they were potentially useful in preserving fresh fruit. You applied for a patent claiming the use of the class of compounds Lambda as a means of preserving fruit, and seek to commercialise this new product. Any patent you obtain is unlikely to be valid, because there is no evidence that you have demonstrated that the invention works in practice. You possibly also may have failed to meet your obligation to describe the invention in full, including how to carry it out in practice.

Is the patent claim for Lambda supported by or fairly based on the disclosure?

To gain a patent for Lambda, you need to give to the public the information necessary to carry out the claimed invention. If you are claiming a scope for Lambda that goes beyond the technological description you have provided, then the claim may be considered invalid. Article 84 of the European Patent Convention provides that patent claims 'shall be clear and concise and be supported by the description.' You cannot broaden your claim to cover material that is not adequately described in the patent document. For example, if you have discovered how to use certain compounds codenamed Lambda to preserve fruit, and describe this in your specification, but include in your patent claims any use of the Lambda compounds to treat or process food in any way, then your claim may not be sufficiently based on your disclosure. For a broader claim to be valid, you would have to describe a wider range of practical applications of the chemicals.

Patentability and other requirements for validity

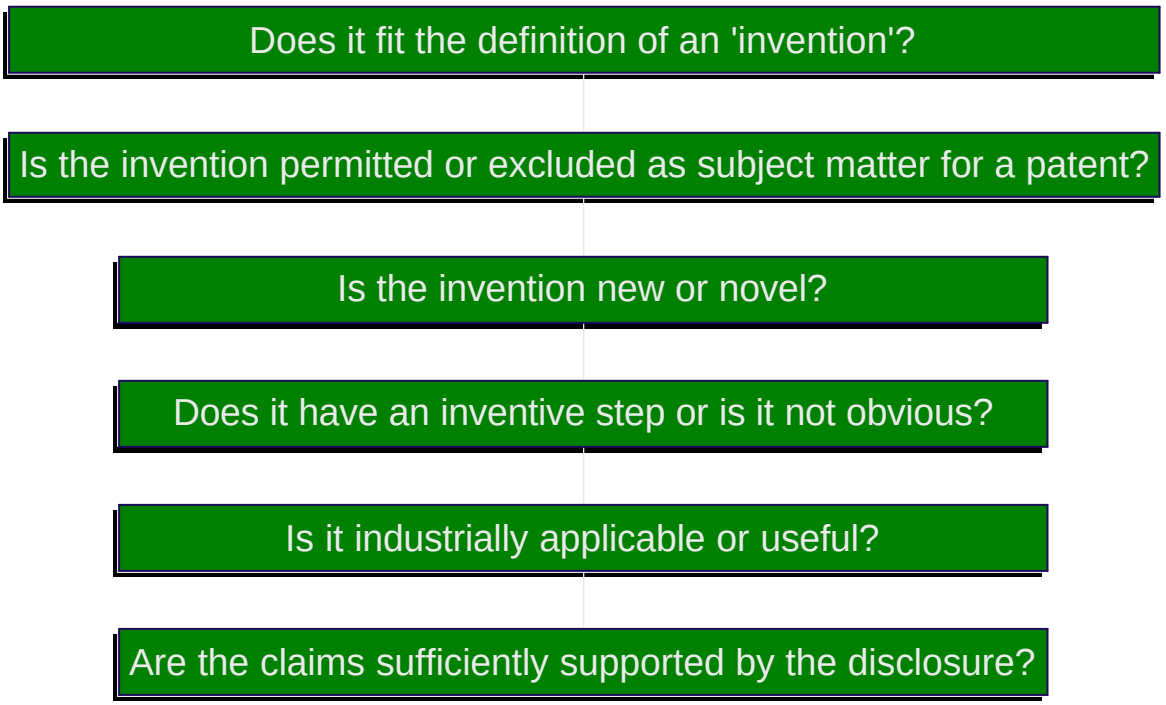
Whether a claimed invention is given a valid patent both on the nature of the invention and on the way the invention is claimed. So the process or product has to meet the requirement of being acceptable subject matter and has to be new, inventive, and industrially applicable. But it also has to be described and claimed correctly – if the description of the invention is inadequate, or if the claims are too broad, then the patent can be held invalid, even if the underlying invention is deserving of a patent. Equally, other deficiencies can cause the patent to be held invalid – if the patent falsely claims that person X is the inventor, when in fact it was person Y.

A granted patent has no guarantee of validity

Each of these tests must be passed for a patent to be valid. The tests are normally applied by a patent office when checking a patent application. But even if a patent is approved and granted by a patent office, there may still be reasons why the patent is not invalid and can be challenged. No patent office, when considering a patent application, can be aware of all possible facts and publications that could make a claimed invention ineligible for patent protection. No patent examiner can ever have access to all relevant documentation. Accordingly, no patent, when granted, carries a firm guarantee that it is valid. It's always possible that further information will come to light that invalidates the patent

For example, US patent 5401504 was granted for the use of the herb turmeric in wound healing. The patent examiner considering this case referred to a number of publications, including earlier patents, in considering this case, but it was considered novel at the time of application based on the information available. However, this patent was subsequently challenged and found not to be valid, because the claimed invention was actually already well known in India and evidence was produced to demonstrate this. This patent is covered in the case studies at the end of this Module.

The steps to take in determining whether a claimed invention is eligible for a patent can be summarised as follows:



2.4 International standards and patents

Even before the conclusion of the WTO Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), there was a strong measure of international harmonisation about what constituted a patentable invention. TRIPS has clarified the existing criteria for granting a patent, and also confined the nature of the exclusions to patentable subject matter that can be applied in national patent laws. TRIPS specifies that patents should be available for inventions, whether products or processes, in all fields of technology, provided that they are new (or novel), involve an inventive step (or are non-obvious), and are capable of industrial application (or are useful).

TRIPS also gives countries flexibility to exclude certain inventions from patenting if it is necessary to protect human, animal or plant life, the environment, public institutions, or morality. Also, TRIPS permits countries to exclude inventions relating to diagnostic, therapeutic and surgical methods of treatment of humans or animals, and plants and animals other than microorganisms.

National approaches to patentability criteria

The requirements of novelty, inventive step and industrial application are fundamental to the conception of a patentable invention almost universally. But TRIPS and the earlier Paris Convention for the Protection of Industrial Property do not specify further how these legal tests for patent protection should work in practice. While there is some consistency in the implementation of these legal tests in laws of countries throughout the world there are also a number of major differences in the way in which these tests are applied. Researchers and patent applicants need to keep this in mind when they are applying for a patent for their inventions in different countries.

In most countries, the patent office will do a preliminary examination for novelty, inventive step and industrial application, although there are some offices that only require the completion of formal processes – in these cases, patents can be subject to examination at a later stage, for example if it is necessary to enforce the patent in the courts. It should be remembered that just because a patent office conducts examination, does not mean that your patent is necessarily valid and not subject to challenges. Almost invariably, when a patent is enforced – in other words, if someone infringes your patent by exploiting your invention, and you take them to court – the other party counter-claims that the patent is invalid, and the patent is subject to very close scrutiny. It is not uncommon for patents to be held invalid as a result of an attempt to enforce them.

If all the tests for patent protection are satisfied in the country in which protection is sought, the applicant is granted a patent by the national patent office. As discussed in *Module 1: Introduction to Intellectual Property*, patent protection provides patentees with limited legal rights to prevent others from using their invention. Patent rights enable patentees to potentially gain commercial benefit from their invention by excluding competitors from using their invention, selling their patent rights or licensing the use of their invention in return for the payment of royalties highlights some of the issues that should be considered in commercialising research.

PCT Guidelines

There are no specific international standards for determining how to apply the key concepts that define what is patentable, such as ‘invention,’ ‘novel,’ ‘non-obvious’ and ‘useful.’ These concepts also need to be sufficiently flexible to cater for emerging technologies, a key issue in the biotechnology field. The detailed consideration of these concepts has largely been determined by the courts dealing with specific patent cases.

At the international level, one valuable point of reference is the Patent Cooperation Treaty (PCT) system administered by the World Intellectual Property Organisation (WIPO). As discussed in more detail in *Module Three: Reading a Patent Document and the Patent Process*, the PCT provides a streamlined process for applying for patents in different countries at the same time. As an optional part of this process, an applicant can request an international preliminary examination. This examination does not have direct legal effect, and does not in itself lead to the patent application being approved or rejected. But it does give the applicant a useful warning of potential problems that they may face in future, before they invest heavily in pursuing the patent further.

The PCT rules for the international preliminary examination therefore give some measure of international agreement as to how the legal tests for patentability can be applied. Even so, it is crucial to remember that this process has no legal significance for the actual outcome of the patent process at a national level, and that national patent law can diverge from the PCT guidelines.

Article 33 of the Patent Cooperation Treaty clarifies the objective of the international preliminary examination as to 'formulate a preliminary and non-binding opinion on the questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), and to be industrially applicable.' This Module refers to the PCT Guidelines to give practical examples of how specific issues arising from the patenting of biotechnology inventions are resolved.

Time is of the essence: the priority date

A fundamental principle of patent law can be summarized as 'first come first served.' It is often the case that researchers are working on similar material at the same time, and can produce similar or even identical results that lead to conflicting claims. The way this is decided comes down to who was the first to take action. Also, a patent right cannot be extended to material that is already in the public domain. You cannot take out a patent on an invention that has already been published or made available to the public. For these reasons, each patent has associated with it a priority date, meaning the date on which it is assessed against other materials – either competing claims for the same invention, or publications or other information that might make the patent invalid.

In many countries the priority date is the date on which the patent application is first filed (in almost all countries the priority date can be backdated to the earlier filing date in another country, provided that it is no more than a year earlier – this is the 'right of priority' provided under the Paris Convention). This is called the "first-to-file" approach. The situation can be different in the US. In the US, the effective priority date, in the case of conflicting applications, is the date of the actual reduction to practice of an invention, which is of course earlier than the first filing date of a patent application. If the inventor is 'diligent' (continuously active in developing the invention), then the priority can date back to the original conception, before the invention is reduced to practice. For any technology that is to be protected in the United States, documenting conception and reduction to practice in laboratory notebooks is a crucial aspect of ensuring effective patent rights.

As a general rule, the priority date of your patent is the date when you lodge the first patent application disclosing the invention. The priority date has two main effects in patent law:

- It establishes the time from which determination of the invention's novelty is determined. Hence, no publication, disclosure or other public activity can affect the validity of your patent if it occurs after the relevant priority date. The state of background technology, and the knowledge of the person skilled in the art, two key issues in determining inventive step, are also assessed as at the priority date.

- If two patent applications for essentially the same invention are received at the patent office (even if the contents of neither one was published at the relevant time), then the one with the earlier priority date is eligible for patent protection, but not the later one. This is because the first application destroys the novelty of the second application, even if the two applicants have had no contact with each other and both independently developed the invention. The chief exception to this is in the 'first to invent' rule is applied, in the US, where the patent with the later filing date could still prevail if the applicant was able to prove first invention (and that they had acted with diligence). Another exception is when two patents for the same subject matter are received on the same day – generally, in this case, both applicants would receive patent rights.

When working with the US 'first-to-invent' system of determining priority, the date of invention can be established by legal documentation, especially laboratory notebooks. This creates a strong practical need for research institutions to consider rigorous record-keeping if there is any possibility of pursuing a patent application in the US. The US is a key market for biotechnology products and processes, and so it is generally advisable to maintain detailed documentary evidence of your inventive process in the suitable format, even though it may not be necessary for your own national patent law.

2.5 What subject matter is patentable?

When assessing whether an invention is eligible for a patent, the first consideration is whether the subject of the claims qualifies as patentable subject matter. Certain claimed inventions may be excluded first because they do not fit the definition of 'invention' or because they fall into certain excluded subject matter. In many countries, legislatures and judges have in some cases decided that – even if something is technically eligible for a patent – it still should not be given a patent, for broader policy reasons. Exactly what subject matter is excluded can differ from country to country.

While TRIPS creates a general presumption that all technologies should be patentable, we have seen how it explicitly provides for the possibility of excluding various categories of subject matter.

Rule 67 of the Patent Cooperation Treaty specifies certain subject matter that the international examination authorities are not obliged to consider. While it must be stressed that this rule has no legal significance in terms of actual patent law at the national level, it does give a useful list of some categories which are considered as potentially not patentable subject matter:

- scientific and mathematical theories;
- plant or animal varieties or essentially biological processes for the production of plants and animals, other than microbiological processes and the products of such processes;
- schemes, rules or methods of doing business, performing purely mental acts or playing games;
- methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods;
- mere presentations of information; and
- computer software in a certain limited context.

The actual approach taken at a national level differs considerably. For example, some countries allow patents for plants and animals that constitute legitimate inventions (such as transgenic plants and animals which are new, the development of which involves an inventive step, and which have some form of useful application). Other countries have specific exceptions for such inventions.

Example - Microorganisms as patentable subject matter

In the US, an important decision confirming the applicability of patent law to microorganisms was the Supreme Court decision in Diamond v Chakrabarty. Chakrabarty had developed a new microorganism, a Pseudomonas bacterium, which degraded hydrocarbons, and so was potentially useful in clearing up oil spills. The US Patent Office had allowed patent claims to the method of producing the bacterium and an inoculum, but objected to a claim of 'a bacterium from the genus pseuodomonus containing therein at least two stable energy-generating plasmids, each of said plasmids providing a separate hydrocarbon degradative pathway.' It rejected this claim on the basis that 'as living things, microbes are not patentable subject matter.'

The Supreme Court overruled this decision and allowed this claim. The court had to consider whether the fact that a bacterium was a living thing was sufficient to exclude it from patent protection. It reviewed the purpose of the patent system, including the statement by legislators accompanying the 1952 Patent Act that Congress intended statutory subject matter to "include anything under the sun that is made by man."

The Court acknowledged that 'the laws of nature, physical phenomena, and abstract ideas have been held not patentable … Thus, a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter. Likewise, Einstein could not patent his celebrated law that $E=mc^2$.; nor could Newton have patented the law of gravity. Such discoveries are *manifestations of . . . nature, free to all men and reserved exclusively to none.*' But the Court decided that the micro-organism 'plainly qualifies as patentable subject matter. His claim is not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter - a product of human ingenuity having a distinctive name, character and use.'

The Court compared this case with an earlier case (Funk), in which "the patentee had discovered that there existed in nature certain species of root-nodule bacteria which did not exert a mutually inhibitive effect on each other. He used that discovery to produce a mixed culture capable of inoculating the seeds of leguminous plants. Concluding that the patentee had discovered "only some of the handiwork of nature," the Court ruled the product non-patentable: 'Each of the species of root-nodule bacteria contained in the package infects the same group of leguminous plants which it always infected. No species acquires a different use. The combination of species produces no new bacteria, no change in the six species of bacteria, and no enlargement of the range of their utility. Each species has the same effect it always had. The bacteria perform in their natural way. Their use in combination does not improve in any way their natural functioning. They serve the ends nature originally provided and act quite independently of any effort of the patentee.'

Here, by contrast, the patentee has produced a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility. His discovery is not nature's handiwork, but his own; accordingly it is patentable subject matter under [US Patent Law]."

Transgenic animals as patentable subject matter

Another significant case concerned the Harvard Onco-mouse. This is a transgenic mouse which has a particular susceptibility to developing cancer. Such as mouse is claimed to be particularly valuable in researching cures for cancer in human beings. The University of Harvard received US patent 4736866 for the invention claimed as 'a transgenic non-human mammal all of whose germ cells and somatic cells contain a recombinant activated oncogene sequence introduced into said mammal, or an ancestor of said mammal, at an embryonic stage.' A mouse produced in this way was described as a preferred embodiment of the invention. The patent document explained the benefits of such animals as useful in testing potential carcinogens, thus minimizing one source of criticism of current methods, that their validity is questionable because the amounts of the tested material used is greatly in excess of amounts to which humans are likely to be exposed.

Equivalent patent applications in the European Patent Office and in Canada were initially rejected by patent examiners. In the EPO, the case revolved around the terms of the European Patent Convention, Article 53, which provided *that European patents shall not be granted in respect of: inventions the publication or exploitation of which would be contrary to ordre public or morality …. [and] plant or animal varieties or essentially biological processes for the production of plants or animals …*

The claims of the EPO patent application included:

1. A method of producing a transgenic non-human mammalian animal having an increased probability of developing neoplasms, said method comprising introducing an activated oncogene sequence into a non-human mammalian animal at a stage no later than the 8-cell stage.

17. A transgenic non-human mammalian animal whose germ cells and somatic cells contain an activated oncogene sequence introduced into the said animal, or an ancestor of said animal, at a stage no later than the 8-cell stage

18. An animal as claimed in Claim 17 which is a rodent.

These claims were rejected by the EPO Examining Division, on the grounds that they claimed animals, which were not patentable under the EPC. Claims 17 and 18 were also rejected because they included further generations or descendants of the animal, which would be produced by biological processes – thus falling within the prohibition on patents on essentially biological processes. As to whether the claimed invention was contrary to morality, the office observed that patent law was not the right legislative tool for resolving the questions of the morality of using animals for testing in this way. In other words, if animal testing using transgenic mice raised ethical issues, these were better addressed by direct legislation rather than indirectly through patent law.

The issue was then considered at the higher review level, by the EPO Technical Board of Appeal, which overturned the decision on these claims. It concluded that the claims were directed to non-human mammals and rodents, and not an *animal variety* as such (which was what the EPC excluded) – in other words, the claim was at a different taxonomic level than an animal variety. It also concluded that the animal was the product of a biological process, not a biological process as such (which was what the EPC excluded). But the Board said that it was correct for the Examining Division to consider the morality test, and remitted the case for reconsideration. The Examining Division considered three different issues that needed to be balanced: the interest of mankind in providing remedies for dangerous diseases; the interest in protecting the environment against uncontrolled dissemination of unwanted genes; and the interest in avoiding cruelty to animals.

It concluded that in this case, the benefits to humanity outweighed the disadvantages: cancer is a frequent cause of death; the invention meant that fewer animals would be needed for testing, thus lowering the overall amount of animal suffering; animal testing is indispensable in cancer research; and the invention does not envisage release into the environment, so the uncontrolled spread of the gene was unlikely. To demonstrate how these issues may be weighed, this case can be contrasted with a similar case concerning a patent application filed by Upjohn for a transgenic hairless mouse that was genetically engineered and bred in order to test restorative products to cure human baldness and wool production techniques. In this instance, the EPO assessed that the advantages of this invention were not so great as to outweigh the ethical disadvantages, and did not allow the patent to be granted.

2.6 How is novelty determined?

Once it is clear that the claimed invention qualifies as patentable subject matter, a fundamental requirement is that the invention should be 'novel' or 'new.' This stems from the principle that patents cannot be extended to material that is already in the public domain. So a patent cannot be valid if it relates to an invention that has already been published, made public or used. This doesn't apply if the invention has been disclosed to someone in strict confidence, because in these circumstances it can't be considered as entering the public domain.

Novelty is destroyed if the invention has been published before the priority date, even in a single document. It is also destroyed if the invention has been performed or exhibited in public, even to one other person, unless confidentiality arrangements have been made. An earlier patent application that discloses your invention destroys the novelty of your application, even if it was not actually published as at the priority date of your application (this is treated as a separate ground for invalidity in some cases – the ground of 'prior claiming' of the same invention). It is irrelevant whether or not you knew about the earlier publication or the previous patent. You can undercut the novelty of your own patent by displaying or publishing your own invention – this has happened time and time again in practice. Novelty can also be undercut if someone else earlier published the same invention independently, whether or not they tried to patent it.

National laws provide various limited exceptions to this rule to take account of some public use of the invention if necessary for experimental and developmental purposes, and other publication by the inventor before the patent application is filed (a 'grace period'). The Cohen-Boyer patent, discussed in Section 2.2 above, was only made possible because of a grace period provision in US law – the invention had already been published in a newspaper before a patent application was filed. But it would have been possible to get a patent for this invention in many other countries because suitable grace periods were not available. Such exceptions are generally very limited, and differ considerably between different countries, so you should check the legal situation very carefully before relying on this kind of exception, especially if you are interested in patent protection in a number of countries.

National laws differ on one further critical question relating to novelty. Some laws take into account only the situation in the country in question: in this case, an earlier public demonstration of the invention in a foreign country would not undermine the novelty of your invention. Other laws base the question of novelty one what happens world wide – an 'absolute novelty' system. In an absolute novelty system, an earlier publication or public demonstration in a foreign country can defeat the novelty of your patent. This is the system, for example, in Europe.

Some systems are mixed, requiring that the invention be novel in relation to publications issued anywhere in the world, but in the case of public use, the prior use has to be in relation to public use only within the country itself. This is the system in many countries.

The PCT international examination guidelines require that 'everything made available to the public anywhere in the world by means of written disclosure (including drawings and other illustrations) shall be considered prior art provided that such making available occurred prior to the relevant date,' in other words, an absolute novelty standard in relation to publication.

Prior Publication

Prior publication occurs when the claimed invention appears in a published document before the priority date of the patent application. This publication may be in the form of a previously published patent or patent application, or it may appear in a journal, usually in a technical journal dealing with the same technical area as the invention. Prior publication includes any document published anywhere in the world. The publication can be any combination of writing, drawings and other illustrations. The important thing is that the publication should disclose to the public how to carry out the invention.

Different countries have different tests for determining whether there has been prior publication of an invention. One test for prior publication is called the "reverse infringement test". Under this test, a claim for patent protection will lack novelty if a document can be found which would infringe the patent claims under consideration.

There are usually a number of requirements placed on the prior art document. The main two are that it contain "clear and unmistakable directions" to do what is claimed and that the document would enable a person skilled in the art to work the invention.

Prior Use

Prior use means that the invention has actually been used in public, quite apart from any published account of the invention. The use can be very limited – for example, in making enquiries of potential commercial partners or research partners. It is not considered prior use if the use was within the terms of a confidentiality agreement, and the use was not seen by any other member of the public not bound by the confidentiality agreement.

This is a crucial consideration in the management of innovation. For example, in one case no more than four copies of a ballpoint pen were distributed for promotional purposes to members of the public before the patent application was filed. There was no evidence that they had taken the pens apart to learn how they worked. This was still counted enough by the court to declare the patent invalid due to prior use of the invention.

In another case, a patent claiming an alloy of steel, containing up to 15% cobalt, was held invalid because another company had made and sold steel containing about 1% cobalt, even though that other company had not publicly disclosed the composition of its product. Anyone purchasing the steel before the date of the patent could have chemically analysed it and found out that it contained a certain proportion of cobalt within the scope of the patent claim.

National patent law can have exceptions to this rule, that allow for novelty to be preserved even in the event of prior use. This might include an exception allowing for use in public for the purposes of research and experiment, where this is impossible without some kind of public disclosure. The Paris Convention (and thus the TRIPS Agreement, which takes in the standards set by Paris) requires that temporary protection be available for patentable inventions 'in respect of goods exhibited at official or officially recognised international exhibitions.'

Example - novelty of a database for genetic information

Bountyquest (http://www.bountyquest.com/infocenter/infocenter.htm) is a Web site that offers rewards to those who find prior publications that might call into question the novelty of certain granted patents. It publishes details of a granted patent, and then invites the public to submit earlier publications that might prove that the patent was not valid due to lack of novelty.

Recently, Bountyquest posted details of US patent 5,966,712 which concerned a relational database system for storing and displaying genetic information. It offered a bounty 'to the first person who submits a document describing a relational database system for storing and manipulating biomolecular sequence information, the database including genomic libraries for a plurality of types of organisms. The system includes a user interface capable of receiving a selection of two or more of the genomic libraries for comparison and displaying the results of the comparison.' The document had to pre-date the priority date of the patent, which was December 12, 1995.

The main claim of the patent was for:

A computerized method of comparing genetic complements of different types of organisms, the method comprising:

(i) providing a database including (open reading frame) sequence libraries for a plurality of types of organisms;
(ii) accepting input for selecting two or more of the sequence libraries for comparison;
(iii) determining open reading frames common or unique to the selected sequence libraries; and
(iv) displaying the results of the determination.

A reward was paid to a German student who submitted two documents he had found on PubMed, an on-line public database of the US National Library of Medicine (www.ncbi.nlm.nih.gov/PubMed/). His search disclosed two articles from the journal Nucleic Acids Research. One, published in 1993, concerned the Ribosomal Database Project and the other, published in 1994, concerned HOVERGEN, a database of homologous vertebrate genes. If you are a biotechnology researcher, can you think of a database of this nature which you used prior to December 1995? How would you prove that the database was published prior to the patent claim?

To find such publications does not amount to a legal determination that a patent is not valid. However, this example is a useful reminder that the grant of a patent is no guarantee that the claims are fully novel, due to the possibility of further prior publications or prior art being found.

2.7 How is inventive step determined?

Reflecting a widely applied principle in national law, TRIPS provides that an invention should involve an inventive step (or not be obvious) in order to qualify for patentability.

Inventive step is a different test to novelty. An invention is novel if it is different from any invention in the prior art. In contrast, an invention involves an inventive step if it would not have been obvious to the person skilled in the art (PSA) at the priority date of the application in view of the common knowledge of the PSA. Key issues are whether the PSA would find the result achieved "surprising" or unexpected and what is considered to be "common general knowledge".

The PCT guidelines indicate that in assessing inventive step or non-obviousness, the question is whether:

> At the relevant date of that claim, it would have been obvious to a PSA to arrive at something falling within the terms of the claim having regard to the art known at that time…. The term 'obvious' means that which does not go beyond the normal progress of technology but merely follows plainly or logically from the prior art, that is something which does not involve the exercise of any skill or ability beyond that to be expected of the PSA.

The PCT Guidelines provides that in considering whether there is inventive step a patent examiner is allowed to combine the disclosures of two or more documents or parts of

documents, different parts of the same document or other pieces of prior art. However, this combining of documents, which is known as "mosaicing", is only allowed where such a combination would be obvious to the PSA. Mosaicing is allowed in a number of countries in determining whether an invention involves an inventive step.

Some examples of inventive step are set out in the PCT guidelines:

(i) The formulation of an idea or of a problem to be solved (the solution being obvious once the problem is clearly stated).

> *Example:* The problem of indicating to the driver of a motor vehicle at night the line of the road ahead by using the light from the vehicle itself. As soon as the problem is stated in this form, the technical solution, viz., the provision of pieces of reflecting glass (or "cats' eyes") suitably positioned and angled along the road surface, appears simple and obvious.

(ii) The devising of a solution to a known problem.

> *Example:* The problem of permanently marking farm animals such as cows without causing pain to the animals or damage to the hide has existed since farming began. The solution ("freeze branding") consists in applying the discovery that the hide can be permanently depigmented by freezing.

(iii) The arrival at an insight into the cause of an observed phenomenon (the practical use of this phenomenon then being obvious).

> *Example:* The agreeable flavor of butter is found to be caused by minute quantities of a particular compound. As soon as this insight has been arrived at, the technical application comprising adding this compound to margarine is immediately obvious.

Who is the person skilled in the art?

The patent examiner needs to apply the concept of the person skilled in the art (PSA) when considering whether an invention satisfies the inventive step test for patenting. Along with the nature of the inventive step itself, the nature of the PSA can be a difficult issue to resolve. The PCT Guidelines say:

> The person skilled in the art should be presumed to be an ordinary practitioner aware of what was common general knowledge in the art at the relevant date. He [sic] should also be presumed to have had access to everything in the "prior art," in particular, the documents cited in the international search report, and to have had at his disposal the normal means and capacity for routine experimentation. If the problem prompts the person skilled in the art to seek its solution in another technical field, the specialist in that field is the person qualified to solve the problem … There may be instances where it is more appropriate to think in terms of a group of persons, for example, a research or production team, than a single person. This may apply, for example, in certain advanced technologies such as computers or telephone systems and in highly specialized processes such as the commercial production of integrated circuits or of complex chemical substances

Factors to consider when determining inventive step

Assessing whether an invention is obvious or not, or is sufficiently inventive to have an inventive step, is one of the most difficult, and subjective, matters for judgment in patent law. In one British case in 1929, a judge commented:

> *Nobody … has told me, and I don't suppose anybody ever will tell me, what is the precise characteristic or quality the presence of which distinguishes invention from a workshop improvement. Day is day, and night is night, but who shall tell me where day ends or night begins?*

Each case is decided according to the specific situation of the invention and technology in question. There are some general principles that have been applied; these include:

- Producing unexpected results: if the invention produces an outcome that goes against the normal expectations at the time, and confounds conventional thinking, then it is more likely to have an inventive quality. Similarly, if it would be assumed that the approach

taken would not work (see the case study on hepatitis B antigen below). It is important to assess this as at the time of the patent's priority date, rather than at the time of examining the patent, because these kinds of breakthroughs tend to reshape thinking about the technology – in other words, making the invention appear obvious in retrospect.

- Solving a long-standing problem: if the problem that the invention claims to solve has been identified for some time, but has resisted solution, then this raises the likelihood that the claimed invention has a true inventive step: if it were obvious, then the long-standing pressure to produce this outcome could have been expected to deliver the solution earlier
- Newly identifying a problem: in some instances, the inventive step largely consists in formulating a technological problem that had not been identified before – in a sense, creating a technological need – even where the actual solution to that problem, once stated, is relatively straightforward. The 'cats eyes' example cited above is an example of such an invention.
- Unrecognised Problem – if the invention in question solves a previously unrecognised problem then this may add weight to a claim of non-obviousness.
- Leaving out one step of an existing practice: an invention may consist in determining that one step of an existing process or practice can actually be omitted, when the person skilled in the art would have assumed that this step is necessary to achieve the outcome.
- Nature of the field of technology: the area of technology, and the general nature of innovative process in that field at the relevant time, may influence judgements as to what is obvious.

The changing nature of routine biotechnology techniques

One of the difficulties in applying the law of inventive step to biotechnology inventions is assessing the common general knowledge. Common general knowledge includes the techniques that would have been known and routine to the PSA at the priority date of the claim.

In well established and slow moving technologies the common general knowledge is decided by reference to basic texts. Techniques are rarely considered routine before they are well recognised as such in the standard texts in the field. Even so, disputes as to whether a given approach is routine in the field are often decided only with reference to experts in the field concerned.

In recent and fast moving technologies, however, it is far more difficult to determine. Biotechnology is a field in which matters that are new and inventive today are frequently routine and obvious in only a few years time. In such circumstances it is possible that currently routine techniques and approaches have not had sufficient time to appear in the standard texts. Furthermore industrial and academic approaches, techniques and equipment used routinely may vary considerably. Also there is increasing use of routine screening techniques and practices which, on the surface, would seem to lead to "obvious" conclusions.

The following case study demonstrates how a period of six months can make all the difference in determining whether an invention is obvious or not.

Case study on inventive step in biotechnology: the Hepatitis B antigen

Biogen v Medeva was an important biotechnology patent case, decided in 1996 by the House of Lords in the UK. It shows how what is inventive and what is obvious can change dramatically in a short space of time. In considering the issue of inventive step or non-obviousness in this case, Lord Hoffman commented:

> Whenever anything inventive is done for the first time it is the result of the addition of a new idea to the existing stock of knowledge. Sometimes, it is the idea of using established techniques to do something which no one had previously thought of doing. In that case, the inventive idea will be doing the new thing. Sometimes, it is finding a way of doing something which people had wanted to do but could not think how. The inventive idea would be the way of achieving the goal. In yet other cases, many people may have a general idea o f how they might achieve a goal but now know how to solve a particular problem which stands in their way. If someone devises a way of solving the problem, his inventive step will be that solution, but not the goal itself or the general method of achieving it.

The Biogen case concerned 'an artificially constructed molecule of DNA carrying a genetic code which, when introduced into a suitable host cell, will cause that cell to make antigens of the virus hepatitis B.' Viral antigens are proteins on the surface of the virus or inside it. When antigens are detected, they trigger the production of antibodies which neutralize the virus. To vaccinate a person against a disease, the isolated antigens for the disease can be artificially introduced into the system, without actually exposing the person to the virus itself, thus stimulating production of the necessary antibodies to defend against later viral attack. The technology in this patent enabled the production of antigens for hepatitis B for use in diagnostic tests for the presence of the disease and in vaccination against the disease.

In 1992, another company, Medeva plc, was planning to market a hepatitis B vaccine made by recombinant DNA technology in colonies of mammalian cells. When Genentech took Medeva to court for infringing its patent, Medeva challenged the validity of the patent (a 'counterclaim' – a very common tactic in cases of patent infringement). One part of the challenge was that the invention was obvious.

There was strong general interest at the time of the invention (1978) in artificially producing hepatitis B antigens. It was known at that time that hepatitis B was produced by a particle (the 'Dane particle') containing a circular DNA molecule (a plasmid), which had two antigens, one at its surface and one at its core. There were three possible ways to obtain the antigens:

- Purification from natural Dane particles – but the quantities available would be limited, and there were safety concerns in dealing with these highly infectious agents
- Synthesize the antigens chemically – but the amino acid structure of the antigens was only partially known
- Produce them through recombinant DNA technology – this required finding the genes that coded for the antigens, and inserting these into a host cell which would express the antigen genes in a form that could be recovered, allowing for ready production of large quantities of the antigen. This meant first finding the necessary genes, and then working out how to insert them successfully into a host cell.

The inventor, Professor Murray, chose the third path, and was the first person to use recombinant DNA technology to produce hepatitis B antigens. He took an approach that seemed unlikely to work in terms of the scientific knowledge at the time. The court weighed the apparent merit of these various options in determining what would have been 'inventive' in 1978. The court also reviewed the state of molecular biology in 1978, particularly the state of knowledge about the DNA structure of the hepatitis B virus, and the techniques of recombinant DNA technology – the methods used to transform the genetic structure of cells.

Biologists distinguish two basic types of cells in organisms – the eukaryotic and the prokaryotic. Eukaryotic cells are more complex and have a distinct nucleus (these are the cells of plants and animals). Prokaryotic cells have a simpler structure, lacking any distinct nucleus and other complex structures (these are the cells of simple organisms such as bacteria). The hepatitis B virus only infects several higher organisms, specifically human beings and some higher primates such as chimpanzees. Its antigens are eukaryotic. In 1978, recombinant DNA techniques were limited to transforming prokaryotic (simple bacterial) host cells (the vectors - or DNA vehicles for inserting the genes into a host cell – suitable for inserting genes into the more complex eukaryotic host cells were still under development). It hadn't been clear whether genetically transformed bacteria could be used to express genes that coded for more complex eukaryotic proteins, such as Hepatitis B antigens. But recently, earlier in 1978, it had been discovered that you could express a DNA sequence for the production of a eukaryotic cell protein (rat preproinsulin) by transforming a prokaryotic bacterium (E.coli) using the recombinant plasmid pBR322 as a vector.

So this suggested that the same kind of technique could possibly work for Hepatitis B antigen. Scientists were divided on whether this new technique would actually be applicable to the genetic engineering of many other eukaryotic genes, or whether it would prove to be a rarity. However, this did at least point to the possibility of using a prokaryotic host and a plasmid vector, making the use of this technology for creating hepatitis B antigens more obvious than it would earlier have been.

There was still a major hurdle. Eukaryotic DNA in its natural state contains gene sequences known as 'introns' whose exact significance is unclear, but they have no role in coding for proteins such as antigens. In the process of transcribing these sequences, a eukaryotic cell removes these introns within its nucleus, and splices together the 'exons' or those parts of the sequences that do code for proteins. It appeared that the simpler prokaryotic cells would not have the same kind of mechanism to strip away introns – they would not appear to need this function. This suggested that the antigen might not be able to be produced in prokaryotic cells, because the technique would need to use natural ('genomic') DNA from the Dane particles, which might have introns (the earlier rat preproinsulin experiment had used artificial eukaryotic DNA from which the introns had already been removed, so it didn't need to deal with the intron problem).

In 1978, scientists still didn't know the structure or location of the genes which coded for the antigen, so they couldn't work out whether or not it had introns. The full genetic sequence of the hepatitis B virus was determined shortly afterwards, in fact six months after the first patent application was filed. It turned out that the hepatitis B virus didn't have any introns. That extra information was enough to make the invention obvious – because anyone working in the field would have seen that there was no obstacle to using prokaryotic cells to reproduce eukaryotic genes that had no introns. But at the time the application was filed, the situation was sufficiently unclear to make this approach non-obvious.

Because, at the time of the invention, he did not have access to the genetic structure of hepatitis B DNA, the inventor took the approach of cutting the Dane particle DNA into relatively large fragments – this would take less time, and would be more likely to keep intact the relevant part of the DNA which coded for the antigen. He then used standard techniques – essentially the rat preproinsulin process – to introduce them into the E.coli bacteria. Certain colonies of these bacteria then tested positively for the required antigen. This method was duly described in the patent application. It claimed that a 'particularly surprising' feature was that genes from eukaryotic organisms wouldn't normally be expressed in bacteria.

Drawing on an earlier court case (concerning a windsurfer patent), the judge indicated that there were four steps in determining obviousness:

- Identify the inventive concept

- Work out what the common general knowledge was at the time, and
- Identify the differences between the inventive concept and matter that was already known or used at the time of the invention
- Ask if the differences are steps which would have been obvious to a person skilled in the art who had no knowledge of the invention

The judges who heard this case at lower levels (the first instance and the initial appeal) had found the patented invention to be obvious. But in the House of Lords, the judge took issue with the way the earlier judges had defined the inventive concept – showing how important it is, when considering non-obviousness, to clarify exactly what the inventive concept is – in other words, the problem which the invention is trying to solve. The judges in the earlier decisions on this case had said the inventive concept was to produce the antigen through recombinent DNA technology; in the light of the rat preproinsulin work, the previous appeal judge found that this inventive concept was obvious.

The House of Lords held instead that the inventive concept was a narrower one: the notion you could produce the antigen by creating large fragments of the genomic hepatitis B DNA, and then using the pBR322 vector to introduce these fragments into the E.coli bacterium – in other words, 'the idea of trying to express unsequenced eukaryotic DNA in a prokaryotic host.' This was not obvious: because of the intron problem and the general uncertainty about the genetic structure, the obvious course would have been first to sequence the DNA. This was a much narrower inventive concept than the one the earlier judges had considered. Of course, this also meant that the scope of the claims that could be supported by this patent was also narrower – an issue that the judge in this case went on to consider (see below).

Research effort and expenditure as indicators of inventiveness

A common argument offered by applicants defending their invention is that it cannot be obvious because it took substantial research effort and expense to create. However, the expense of research does not determine whether an invention is obvious or not, and the fact that an applicant has spent a great deal of time and money in achieving a certain result does not mean that invention involves an inventive step, nor is necessarily patentable.

The skills of the examiner in a rapidly moving field

As an examiner working in the biotechnology field, there are a number of issues that affect the extent to which he or she can bring technical competence to the examination.

Patent examiners find determining common general knowledge in biotechnology particularly difficult. Although they see routinely the cutting edge of the field, examiners are not directly involved in the routine activities in the laboratory. It is therefore not possible for them to know with certainty the extent of the common general knowledge in this fast growing and diversifying field. The good news for patent applicants is that any doubt in the mind of the examiner is resolved in favour of the applicant.

Dated technical qualifications

Over time an examiner's qualifications and experience become less relevant to the technical content of the material to be examined. A patent office and its employees therefore have to take steps to update the examiners technical skills in an attempt to keep pace with changing technology.

Experience in a narrow technical specialty

Similarly, technical training is frequently in a very narrow area. Patent examination is rarely limited to such narrow technological divisions. Again, some level of re-training may be

necessary to allow the examiner to become competent in the broader technologies to which they now have regard.

In very large patent offices, such as the US and Europe offices, examiners may be able to specialise in the particular narrow field in which they were originally trained. Even so, traditional divisions between technologies are moving and changing. Frequently the specialised training that was highly relevant a few years ago has, by today, become merely a part of the technical background required to comprehend the technologies that are evolving.

2.8 How is 'usefulness' determined?

One condition under TRIPS for an invention to be eligible for a patent is that it be capable of industrial application (or be useful). The PCT specifies that, for the purposes of the international preliminary examination, 'a claimed invention shall be considered industrially applicable if, according to its nature, it can be made or used (in the technological sense) in any kind of industry. *Industry* shall be understood in its broadest sense, as in the Paris Convention for the Protection of Industrial Property.' The Paris Convention provides that:

> Industrial property shall be understood in the broadest sense and shall apply not only to industry and commerce proper, but likewise to agricultural and extractive industries and to all manufactured or natural products, for example, wines, grain, tobacco leaf, fruit, cattle, minerals, mineral waters, beer, flowers and flour. (Paris Article 1(3))

The PCT Guidelines state that 'industry includes any physical activity of a technical character, that is, an activity which belongs to the useful or practical arts as distinct from the aesthetic arts.' An invention is likely to be capable of industrial application if it is a useful product or process. The PCT guidelines clarify that industry 'includes any physical activity of a technical character, that is, an activity which belongs to the useful or practical arts as distinct from the aesthetic arts; it does not necessarily imply the use of a machine or the manufacture of an article and could cover a process for dispersing fog, or a process for converting energy from one form to another. If any product or process is alleged to operate in a manner clearly contrary to well-established physical laws and thus the invention cannot be carried out by a person skilled in the art, objection could arise because the description and claims are so unclear that no meaningful opinion can be formed.'

The United States Patent and Trademark Office (USPTO) recently issued revised examination guidelines for utility of claimed inventions. These guidelines stipulate that an invention has 'well-established utility'

> (1) if a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention *(e.g.,* properties or applications of a product or process), and
>
> (2) the utility is specific, substantial, and credible.

The development of these guidelines involved extensive consultations on biotechnology patenting issues: a report on these consultations is reproduced in *Annex Two* of this Handbook, together with the guidelines themselves.

A Mere Discovery and the Meaning of "Naturally Occurring"

In the international debate about the patenting of biological material and derivatives of biological material (such as specific DNA sequences), the issue often arises as to whether patents are being granted, or should be granted, for material that appears to be naturally occurring and has simply been discovered. The example earlier given in this module, of the human hormone adrenalin, which was patented in the early 1900s, raised this issue. The hormone obviously existed in nature, but its isolation for possible therapeutic use was a new

state of affairs which was potentially useful in a practical sense. The judge in this case, in 1911, concluded that:

> even if it were merely an extracted product without change, there is no rule that such products are not patentable. Takamine was the first to make [adrenaline] available for any use by removing it from the other gland-tissue in which it was found, and, while it is of course possible logically to call this a purification of the principle, it became for every practical purpose a new thing commercially and therapeutically. That was a good ground for a patent.

In this case, it was not adrenalin as such that was patented, but its artificially extracted and isolated form. A patent claim for adrenalin in its natural environment, that is within the human suprarenal gland, would obviously be invalid, not least because it is not novel.

More recently, the European Parliament and Council has issued a directive on patenting of biotechnology which states that:

> Biological material which is isolated from its natural environment or produced by means of a technical process may be the subject of an invention even if it previously occurred in nature.

In general, patent law requires that a patentable invention must result in (or from) an artificially created state of affairs – a patent claim should not cover something that already occurs in nature and is a simple discovery of that thing. It would both be not 'novel' in the sense that it was already in existence at the date of the patent claim, and it would not have the quality of an invention. The distinction between a discovery and an invention was clearly expressed in an English case in 1902:

> Discovery adds to the amount of human knowledge, but it does so only by lifting the veil and disclosing something which before had been unseen or dimly seen. Invention also adds to human knowledge, but not merely by disclosing something. Invention necessarily involves also the suggestion of an act to be done, and it must be an act which results in a new product, or a new result, or a new process, or a new combination for producing an old product or an old result.

Accordingly, an organism that is "naturally occurring" or an organism just in the form in which it exists in its natural environment cannot in itself be an invention. Patents are not granted for such materials unless it can be demonstrated that the form of the organism as claimed is different from the naturally occurring form. For example, a naturally occurring plant or microorganism that is first discovered or formally identified by a scientist could not be the subject of a patent claim. This is different from a new plant which is created from a non-obvious process of selective breeding, cross-breeding or genetic engineering, or a microorganism which is purified in an inventive way for some productive use in a form that does not exist in nature. So a patent might in theory be granted for a new plant developed through human intervention, or for a microorganism removed from its natural environment in an isolated and purified form. It would still be necessary, however, to demonstrate that all the other criteria for patentability applied – i.e. that it was novel, inventive and industrially applicable.

Essentially, for a patent to apply to a life form, there must be some demonstration of inventive human intervention in its claimed form. At the same time, a number of countries have elected specifically to exclude patents on higher life forms (plants and animals other than microorganisms), regardless of whether they would otherwise qualify as inventions.

This issue also arises in relation to patents on genetic material. On one hand, the determination of a gene sequence could be argued to be a simple discovery of a situation already occurring in nature. On the other hand, it could be argued that a gene sequence in isolation is not something that occurs in nature, and it can new and yield useful results. According to US patent law, 'whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of [the patent law].' The recent USPTO guidelines observe that 'an inventor's discovery of a gene can be the basis for a patent on the genetic composition isolated from its natural state and processed through

purifying steps that separate the gene from other molecules naturally associated with it.' The guidelines distinguish two illustrative cases:

- a patent application only disclosing the nucleic acid molecular structure for a newly discovered gene, with no utility for the claimed isolated gene – this would not be patentable
- such a patent application in which the inventor also discloses a use of the purified gene isolated from its natural state – this could be eligible for a patent

According to these guidelines, a patent may be granted for an isolated and purified gene composition, if the patent application 'discloses a specific, substantial, and credible utility for the claimed isolated and purified gene.' The guidelines discuss a case dealing with the prostaglandins PGE2 and PGE3, extracted from human or animal prostate glands:

> A patent examiner had rejected the claims, reasoning that ''inasmuch as the 'claimed compounds are naturally occurring' … they therefore 'are not 'new' within the connotation of the patent statute.' '' … The Court reversed the Patent Office and explained the error: ''what appellants claim—pure PGE2 and PGE3—is not 'naturally occurring.' Those compounds, as far as the record establishes, do not exist in nature in pure form, and appellants have neither merely discovered, nor claimed sufficiently broadly to encompass, what has previously existed in fact in nature's storehouse, albeit unknown, or what has previously been known to exist.'' … Like other chemicals eligible for patenting when isolated from their natural state and purified, and when the application meets the statutory criteria for patentability. The genetic sequence data represented by strings of the letters A, T, C and G alone is raw, fundamental sequence data, i.e. nonfunctional descriptive information. While descriptive sequence information alone is not patentable subject matter, a new and useful purified and isolated DNA compound described by the sequence is eligible for patenting, subject to satisfying the other criteria for patentability.

The European Union directive, cited above, also suggests that the simple act of discovering gene sequences should not be patentable

> It is important to assert the principle that the human body, at any stage in its formation or development, including germ cells, and the simple discovery of one of its elements or one of its products, including the sequence or partial sequence of a human gene, cannot be patented … a mere DNA sequence without indication of a function does not contain any technical information and is therefore not a patentable invention

This debate continues. For example, it is one of the issues raised in the case study on Relaxin, in *Module Six*.

Is Patenting of Life Forms Allowed?

In principle, TRIPS provides for the protection of inventions in all fields of technology whether or not the field of technology deals with living organisms. However, TRIPS does permit certain plants and animals, other than microorganisms, to be excluded from patenting, as well as essentially biological processes. TRIPS also allows inventions to be excluded from patenting if it is necessary to protect human, animal or plant life, the environment or morality.

As we have noted in *Module One*, various approaches have been taken in different countries on patenting of higher life forms, and to take account of moral issues. For example, the European Patent Convention (EPC) provides that patents for animal and plant varieties are specifically excluded (EPC Article 53(b)). Also, the European Patent Office will not grant patents containing claims to the treatment of a human being via biological or other means. In Australia, for example, the Patent Act 1990 (s18(2)) allows patenting of inventions using microorganisms, plants and animals but not human beings and the biological processes for their generation. The Chakrabarty and Harvard Oncomouse examples discussed above indicate some of the issues that have been raised in relation to patenting live organisms.

2.9 What other requirements are there?

Enabling Disclosure

Requirement of Full Description of an Invention

The philosophy of the patent system is that monopoly patent rights are granted to an inventor in exchange for details of how the invention works. The details of an invention are called the "enabling disclosure" and are included in the complete specification lodged with the patent office.

The requirement of full description of an invention is a TRIPS obligation. TRIPS provides that:

> An applicant for a patent shall disclose the invention in a manner sufficiently clear and complete for the invention to be carried out by a person skilled in the art and may require the applicant to indicate the best mode for carrying out the invention known to the inventor at the filing date or, where priority is claimed, at the priority date of the application.

As with many other tests for patenting, the implementation of the requirement of full description of an invention differs between countries, but the effect is similar. Essentially, the requirement of full description involves an enabling disclosure including a "best method of performance". This means that the applicant must provide at least one example (the best, but not necessarily the only example) of the performance of the invention. Further, the enabling disclosure must disclose in sufficient detail the invention to enable a PSA to perform the invention without additional inventive activity.

Different inventions have different requirements of full description. For example, in Australia the requirement for full description in the case of an organism means that an inventor must provide "full morphological, biochemical and taxonomic description". In the case of flowers and flower parts this may also require the filing of colour photographs. Such descriptions can be quite onerous on the applicant. In the case of some organisms, such requirements for description might still be insufficient to describe the invention to the extent that it can be readily distinguished from other organisms that are not the invention.

Deposit of Microorganisms under the Budapest Treaty

The difficulties facing inventors in fully describing their inventions dealing with microorganisms led to the negotiation of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure (the Budapest Treaty).

This treaty allows patent applicants to deposit the microorganism referred to in their invention at a recognised international depositary. This deposit satisfies the requirement in patent law that an invention be fully described. The Budapest Treaty ensures that the description satisfies these requirements by allowing access to the microorganism deposited.

What is a microorganism?

The WIPO Guide to the Deposit of Microorganisms under the Budapest Treaty defines the term "microorganism" to include any microscopic biological material or life-form. In practice, whether an entity technically is or is not a microorganism matters less than whether the deposit of that entity is necessary for the purpose of sufficiency in a patent application and whether an international depositary authority (IDA) prescribed under the Treaty will accept it. Thus, for example, tissue cultures, plasmids and even seeds have been deposited as micro-organisms under the terms of the Treaty.

Biotechnology Inventions must be Repeatable

The requirement for an enabling disclosure means that the disclosed invention must be repeatable. That is, a PSA must be able to repeat the steps in the description and reproduce the invention. When an invention requires the combination of individual components, such as in chemistry and engineering inventions, the requirement of repeatability provides few difficulties.

However, in biotechnology the invention may follow from an extensive period of cross-breeding and complex screening steps. Under such circumstances the probability of repeating the invention, even using the best method known to the applicant, can be very low. In such cases, the issue for the patent examiner is not simply the numeric probability of achieving the specified result, but whether the result can be reproduced to a practical level acceptable to the person skilled in the art.

For example, some microbiological work done under automation and/or computer control over a period of time involves millions of trials. In these fields such a number is clearly practical and can meet the requirement that an invention is repeatable.

On the other hand, the numeric probability of repeating an invention can be so low that it does not satisfy the requirement that an invention be repeatable. For example, the method of production for the Scarlet Queen Elizabeth rose was a chance genetic mutation. It was estimated that the probability of repeating this mutation was 1 in 100,000,000, which was impractical, if not impossible. As a consequence, the process of production of the plant was not sufficiently described.

Claims supported by the description

It is crucial to the underlying fairness of the patent system that no-one should be given patent rights that go beyond the effective value of the disclosure they have made to the public through the descriptive part of the patent document. If the claim goes significantly beyond the material disclosed in the patent document, the effective patent right would exceed the entitlement of the patent holder, given that the patent is in effect a deal between the inventor and the state, exchanging limited exclusive rights for full disclosure of the invention. To have a valid patent therefore requires a suitable balance between the claims (which define the rights obtained) and the description of the invention (which serves to inform the public how to carry the invention out). Reflecting similarities with the practice in many national patent systems, the PCT system states that patent claims must:

(i) “define the matter for which protection is sought”;

(ii) “be clear and concise”; and

(iii) “be fully supported by the description.”

The PCT guidelines provide that:

> most claims are generalizations from one or more particular examples. The extent of generalization permissible is a matter which the examiner must judge in each particular case in the light of the relevant prior art. Thus, an invention which opens up a whole new field may be entitled to more generality in the claims than one which is concerned with advances in a known technology. An appropriate claim is one which is not so broad that it goes beyond the invention nor yet so narrow as to deprive the applicant of a just reward for the disclosure of his invention. Obvious modifications and uses of and equivalents to that which the applicant has described should not be questioned. In particular, if it is reasonable to predict that all the variants covered by the claims have the properties or uses the applicant ascribes to them in the description, it is proper for the applicant to draw his claims accordingly.
>
> As a general rule, a claim should be regarded as supported by the description unless, exceptionally, there are well-founded reasons for believing that the skilled man would be unable,

> on the basis of the information given in the application as filed, to extend the particular teaching of the description to the whole of the field claimed by using routine methods of experimentation or analysis. Support must, however, be of a technical character; vague statements or assertions having no technical content provide no basis.
>
> An example of this might be a claim to a specified method of treating "synthetic resin moulding" to obtain certain changes in physical characteristics. If all of the examples described related to thermoplastic resins, and the method was such as to appear inappropriate to thermosetting resins, then restriction of the claims to thermoplastic resins might be necessary.

A patent applicant usually drafts the claims in their patent application broadly to prevent any competitor from making, using or selling a very similar product that makes use of the essence of the invention. But claims that are drafted too broadly can be overturned, making the patent invalid. Striking this balance is a key professional requirement of the patent attorney.

In biotechnology this becomes an issue when the nature of an invention is not well understood even by the inventor. For example, in recombinant DNA technologies, geneticists are aware that genes are bounded by codons that indicate the beginning and end of a gene, and codons that switch a gene on and off. How this occurs is still not clearly understood. So when a biotechnologist inserts a gene for blue colouring into a sunflower, for example, and the sunflower expresses the blue colouring, it is not necessary for there to be a detailed explanation of how the sunflower switches 'on' the blue colouring. That this technique actually works is usually sufficient. Under such circumstances the applicant often drafts claims by result. This can give rise to fair basis difficulties where the claim is a mere restatement of the desired outcome of the research. An example could be:

> A nucleotide sequence or fragment thereof which encodes a protein capable of binding to one of a family of receptors to achieve a desired biochemical or pharmaceutical result.

As noted above, the PSA must be able to perform the invention based on the enabling disclosure in the patent specification without a level of experimentation that amounts to invention. Claims in a patent specification need to be drafted so that the PSA would not be forced to carry out extensive experiments to determine if they are infringing and/or to determine the scope of the monopoly of the claim in question – this is known as an 'undue burden of experimentation' on the person to whom the patent disclosure is addressed.

Example: Breadth of claims for cloning Hepatitis B antigen

The Biogen v Medeva case (discussed above in the section on 'inventive step') related to a claim for a recombinant (genetically engineered) DNA molecule which had the genetic code for the hepatitis B antigen; the patent described how the inventor had produced this result by an unexpected means, avoiding the need to find out the actual genetic sequence of the whole hepatitis B virus particle.

The House of Lords also considered whether this claim was supported by the disclosure of the patent, in other words whether the breadth of the claim exceeded the technical contribution to the art made by the invention described. The judge held that it was inevitable in a young science that dramatically new things – like cloning Hepatitis B antigen – 'would be done for the first time. Those who followed, even by different routes, could have greater confidence by reason of the initial success, but this was not enough to justify a monopoly over the whole field. Care was needed not to stifle further research and healthy competition by allowing the first person who had found a way of achieving an obviously desirable goal to monopolise every other way of doing so.'

So even though the invention appeared to be non-obvious (as well as being novel and useful), the patent was held to be invalid because the claim was too broad and was not supported by the disclosure. 'The technical contribution to the art disclosed [in the patent] consisted in showing that – despite the uncertainties which then existed over the DNA of the Dane particle – known recombinant techniques could be used to make HBV antigens in a prokaryotic host cell. This did not justify a claim to a monopoly of *any* recombinant method of making the antigens. The claimed invention was too broad. Its excessive breadth was due, not to the inability of the teaching to produce all the promised results, but to the fact that the same results could be produced by different means which owed nothing to the invention. It did not establish any new principle which other would have to follow to achieve the same results.'

In other words, if another person had cloned hepatitis B antigen through another method – such as one based on sequencing the Dane particle DNA – this would have fallen within the scope of this patent, even though the patent would provide no real guidance to that person.

2.10 Concerns over Biotechnology Patents

The use of biotechnology to create genetically modified organisms raises controversial issues that society and governments need to address. These concerns range from the ethical to concerns of health and environmental safety of biotechnology developments. The patent system is often criticised as being the cause of these concerns. It is important to distinguish the limited nature of a patent right over a biotechnology invention, the regulatory system under which a patent right can be exercised and issues that arise from biotechnology itself.

Biotechnology Patents Rights and the Regulation of Biotechnology

Patents give the patentee the limited right to exclude others from using their invention. A patent does not mean that a patentee can automatically exploit the invention. Many inventions are subject to restrictions on their use, including prohibition. For example, you may develop and patent a new pharmaceutical. But health regulations may require that you subject your invention to extensive testing and trials to ensure its safety before you can market your medicine. There is no guarantee that you would ever be permitted to supply your pharmaceutical to the public – whether or not you had a patent. The need for rigorous testing is one reason why it can take so long between a scientific and technical breakthrough in medical treatment and its widespread market availability. Similarly, if you develop and patent a new herbicide, it too may have to be subjected to extensive testing and trials to ensure that it complies with environmental regulations. Biotechnologies are also subject to health and environmental controls that are outside the patent system as such

All a patent does, is to recognise that the claimed invention is an invention for the purposes of patent law, and gives the right to exclude others from exploiting the invention without appropriate permission from the right holder. A patent does not guarantee that the patentee, or anyone else can use the patented technology. It must be remembered that a patented technology is also subject to regulatory frameworks that domestic governments may put in place.

There are concerns about the impact of biotechnology on many areas including health, the environment, biodiversity, access to genetic resources, ethics, indigenous and local communities, and farmers' rights. It is therefore appropriate that these issues be considered by the relevant regulatory frameworks. This is currently happening in a number of areas.

The possible health and environmental risks arising from genetically modified organisms are being addressed by Governments around the world. For example, the Cartagena Protocol on Biosafety to the Convention on Biological Diversity (CBD), which was opened for signature in May 2000, deals with these issues. The objective of the Protocol is:

> To contribute to ensuring an adequate level of protection in the field of the safe transfer, handling and use of living modified organisms resulting from modern biotechnology that may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health, and specifically focussing on transboundary movements.

Also under the CBD, work is being done on a range of other issues including the rights of indigenous and local communities, and farmers' rights.

The United Nations Food and Agriculture Organisation (FAO) is working to address issues relating to access to genetic plant resources in various ways. In particular, the FAO recently concluded the International Treaty on Plant Genetic Resources for Food and Agriculture.

The intellectual property standards established under TRIPS do not impede the right of a country to impose regulations or controls on the use of technology. It is normal for a patented pharmaceutical to be approved for actual use many years, even more than a decade, after the patent application is made. In the absence of approval from the health authorities, it is impossible to use a new pharmaceutical, even if the pharmaceutical has been patented. Some patented candidates for regulatory approval may never be approved for use at all. In general, a technology that is deemed unsafe, hazardous to health or the environment can be banned or otherwise regulated, whether or not it is considered a patentable invention. Even so, TRIPS gives countries flexibility to deny patents to inventions, when using the invention would be contrary to human, animal or plant life, the environment or morality. Also, TRIPS allows countries to exclude inventions relating to diagnostic, therapeutic and surgical methods of treatment of humans or animals and plants and animals other than microorganisms.

The recent EU directive on biotechnology inventions (*Annex Three* to this Handbook) gives some specific examples of inventions that would be considered contrary to ordre public or morality, and thus ineligible for patents:

> (a) processes for cloning human beings;
>
> (b) processes for modifying the germ line genetic identity of human beings;
>
> (c) uses of human embryos for industrial or commercial purposes; and
>
> (d) processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes.

The Harvard Oncomouse and Upjohn cases discussed above show how assessments on ethical issues in relation to patents have been made.

2.11 Summary of Module Two

Practice of biotechnology

Biotechnology inventions are growing in importance to many industries including the:

- pharmaceutical industry, eg, genetically engineered human insulin
- agricultural industry, eg, genetically modified plants resistant to disease and pests.

Basic patent concepts

- **prior art**: published documents anywhere in the world and common general knowledge in the field of technology of the invention before the priority date of the patent application.
- **priority date:** the date at which an invention's validity is assessed – normally, the date of the first time an application for the invention is filed anywhere in the world. In the US, an earlier date of actual invention can prevail.
- **person skilled in the art (PSA)**: a skilled technician or worker in a field of technology who is aware of all the common laboratory or workshop techniques and general knowledge in the field.

Tests for whether an invention can be patentable

National patent laws provide for patent protection of an invention that is:

- **novel**: that is, it was not published or used before the priority date of the invention.
- **involve an inventive step**: that is, it would not have been obvious to the PSA at the priority date of the application in view of the common knowledge of the PSA.
- **capable of industrial application / useful**: that is, it has to achieve some useful function in any kind of industry, and bring about the results claimed for it.
- **fully described in the patent specification**: that is it must be fully described, including the best example of how to perform the invention.
- **the Budapest Treaty on the Deposit of Microorganisms** makes it easier for inventors to provide a full description of their invention when it involves a microorganism. An inventor can deposit the microorganism with a recognised international depositary rather than describe it in writing.

Finally the claims in a patent specification must be **supported by** or **fairly based** on the description of the invention so that the invention without undue experimentation.

Specific exceptions to patent rights are provided for **public policy reasons** – these can apply to inventions which would contradict morality, or damage health or the environment; some countries elect for policy reasons not to allow patents for new plants and animals created by an inventor, even where these would otherwise be eligible for patents.

Ethical and social aspects of biotechnology patents

Regulatory bodies such as Government health and environment departments and international organisations (eg, Food and Agricultural Organisation) and treaties (eg, the Convention on Biological Diversity) address concerns about linkages between biotechnology and health, environment, biodiversity, access to genetic resources, ethics, indigenous and local communities, and farmers' rights. Patent rights are exclusionary, rather than positive entitlements to use a patented invention, and use of the invention is subject to regulatory frameworks.

2.12 Group Exercises - Module Two

Module Two sets out information about the patenting of biotechnology inventions. Please discuss Module Two with your fellow participants and consider the following questions. You can use these questions to structure group discussions, or write out individual answers to the questions. Please write down the relevant TRIPS Articles where appropriate (the text of TRIPS is available at *Annex One* of this Handbook). Following these questions are two longer case studies that look at particular patents.

Exercise 2.1 - patentable subject matter

Noor is a biotechnology researcher. After many years of research she has worked out how to genetically manipulate the genetic structure of carnations to create a new variety of green flowers. Do you think that Noor could get a patent for this invention? Why? What conditions would Noor's invention have to satisfy to be eligible for a patent?

Exercise 2.2 - patentable subject matter

Budi, a biologist, recently went on a scientific expedition in Sarawak. In the jungle he found a naturally occurring herb that had never been identified before. After noticing that the plant helped ease the effects of skin irritation caused by other plants, he found that it could also be used to ease the symptoms of asthma. Do you think that Budi could get a patent for the herb plant - or for its use as a method of treating skin rashes or asthma? Why? What kind of input would Budi need to make in order to create an invention eligible for a patent? What kind of exceptions to patent rights might apply?

What kind of permission do you think Budi would need to take the plant from the jungle - from local or indigenous communities, from the provincial or national government? What would be the situation if his discovery of the beneficial properties of the plant used local traditional knowledge about the properties of similar herbs?

Exercise 2.3 - patentable subject matter

What are the possible legal reasons for preventing the patenting of a cloned human being?

Exercise 2.4 - full description and the Budapest Treaty

Achmad has invented a new plant variety of wheat using a genetically modified organism. He wants to get a patent for his invention. He knows that to get a patent he has to fully describe his invention in his patent application. He finds it very hard to describe the microorganism in his invention. Can Achmad satisfy the requirement of full description without describing the microorganism in writing? How?

Exercise 2.5 - fair basis, novelty and inventive step

My Hanh has developed a new variety of rice with increased yield, and resistance to a common pest of rice plants. My Hanh believes that this variety will help her country to provide more food for its people and be able to export increased quantities of high quality rice, while reducing expenditure and use of chemical pesticides.

My Hanh wants to get intellectual property protection for her new variety. What are the various options that might be open to her? If patent protection is available, what would she need to say in her patent application to make sure that she satisfied the patent requirements of novelty, inventive step and utility?

Exercise 2.6: Biotechnology, genetic resources & IP: turmeric patent

This case study concerns US patent document 5,401,504 *Use of turmeric in wound healing*. Extracts from this patent are reproduced below. Consider the patent description, and refer also to the text of the TRIPS Agreement in *Annex One*. *Turmeric* is both a plant (*curcuma longa*, from the ginger family) native to India, and a ground powder, prepared from the plant's rhizomes (underground stems), which is a spice very widely used in Indian cooking. According to the patent document, 'turmeric has long been used in India as a traditional medicine for the treatment of various sprains and inflammatory conditions.'

A manufactured product, a skin cream put on the market by Vicco Laboratories, an Indian company based in Goa, has the following description on its packaging:

> Vicco® turmeric skin cream
> Ayurvedic medicine (for external use only)
> Vico Turmeric, an Ayurvedic Medicine, prevent and cures skin infections, inflammation, blemishes, wounds and other skin disorders. It sooths boils, pimples, acne and burns. It nourishes the skin, improves tonal value and makes it fair and beautiful.
> Contains:
> Extract of Turmeric 16%
> Sandalwood oil 1.2%
> (in a non-greasy base)

One dictionary definition of 'Ayurveda' is 'basically naturopathic system of medicine widely practised in India, and based on principles derived from the ancient Hindu scriptures, the Vedas. Hospital treatments and remedial prescriptions tend to be non-specific and to coordinate holistic therapies for body, mind and spirit.'

- What is the actual scope of the claims, and what does the description identify as the nature of the invention? What problem does the invention aim to solve?

TRIPS Article 27.1:

Is the patent a patentable invention in terms of Article 27.1

- Is it new?
- Does it involve an inventive step or is it non-obvious?
- Is it capable of industrial application?

In assessing novelty, consider:

- the description of the use of turmeric in the patent description
- the package of medicinal cream

In assessing non-obviousness, consider:

- The properties of turmeric described in the patent document
- The description of the usage of the package of medicinal cream
- Who would be the person skilled in the art?

Why would you need to check when the Vicco ® product was first put on the market, or first entered production? What is the crucial date for the patent's validity?

Article 27.2:

Is it possible to deny protection to this patent under any of the grounds given in this paragraph?

Article 27.3

Is it possible to deny protection to this patent under any of the grounds given in this paragraph?

Article 28

What would be the effective scope of this patent?

How could this patent be enforced?

Would the manufacture and sale of the skin cream fall within the scope of the patent rights? What if the skin cream was only produced and sold outside the United States?

Other issues:

- Does this patent make use of traditional knowledge?
- How can such traditional knowledge be recorded and documented?
- How can such traditional knowledge be protected? What sort of financial or other benefits could be made available to those who have preserved this

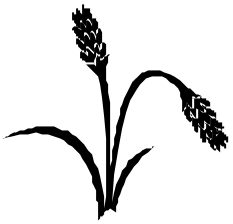
Documentation of traditional knowledge

This case, at first instance, partially hinges on the scope of documentation that is available to the patent examiner, and this in turn depends on the degree to which traditional knowledge about the properties of natural products have been formally documented. The field of ethnobotany is defined (Oxford English Dictionary) as 'the traditional knowledge and customs of a people concerning plants; the scientific study or description of such knowledge and customs.' There are many publications and collections of data in this area. For example, a search on the Phytochemical and Ethnobotanical Databases at the Agricultural Research Service (at http://www.ars-grin.gov/duke) offers an ethnobotany query which provides indications of therapeutic uses of many plants. Searching for turmeric or 'Curcuma longa' produces the following entries:

> Abscess Burkill,1966; Amenorrhea Burkill,1966; Cold Burkill,1966; Conjunctivitis Burkill,1966; Cosmetic Burkill,1966; Diarrhea Burkill,1966; Diuretic Burkill,1966; Dysentery Burkill,1966; Gonorrhoea Burkill,1966; Gravel Burkill,1966; Hepatosis Burkill,1966; Jaundice Burkill,1966; Lactagogue Burkill,1966; Parturition Burkill,1966; Pyuria Burkill,1966; Scabies Burkill,1966; Sore Burkill,1966; Swelling Burkill,1966; Tonic Burkill,1966; Urogenital Burkill,1966; ***Wound Burkill,1966***
>
> Amenorrhea Uphof; Antibilious Takeda; Balsamic Takeda; Bite(Leech) Uphof; Bruise Uphof; Catarrh Uphof; Chickenpox Uphof; Cholagogue Keys; Cold Uphof; Colic Uphof; Congestion Uphof; Depurative Singh; Dermatosis Singh; Escharotic Uphof; Fumitory Uphof; Hemostat Keys; Smallpox Uphof; Stomachic Keys, Takeda; Vulnerary Uphof; ***Wound Uphof***

- What implications does this information have for the validity of the patent?
  - Do you consider that it affects the novelty of any of the patent claims?
  - Do you consider that it affects the non-obviousness (or inventive step of any of the patent claims?
  - Is it significant that the database entry does not mention:
    - How the plant is used to treat the complaint (e.g. orally or topically)
    - Its potential use for ulcers in particular (see claim 6)?
- What are the relevant dates? How would you establish when this information was available to the public?

Exercise 2.7: Biotechnology, genetic resources & IP: Basmati rice patent



This exercise concerns US patent ***5,663,484, Basmati rice lines and grains.*** Extracts of this patent document are provided below in the annex to this module.

Basmati is a variety of rice traditionally grown in the Punjab region of India and Pakistan.

The Merriam-Webster dictionary (which concerns US usage) defines *basmati* as 'a cultivated aromatic long-grain rice of South Asian origin' and gives the origin of the word as 'Hindi *bAsmatI* kind of rice, literally, something fragrant.' It is also suggested that 'basmati' is an ancient word derived from a Sanskrit term for 'fragrant earth.' It is not a geographical place name.

The patent document notes that "good quality basmati rice has a unique combination of characteristics. Good quality basmati rice has a distinctive and pleasant aroma, long slender grains, extreme grain elongation on cooking, and a dry, fluffy texture when cooked."

The patent document notes that "in some countries the term *basmati rice* can be applied to only the basmati rice grown in India and Pakistan," including the UK and Saudi Arabia, which are major markets for basmati rice. The qualities of basmati rice are attributed to the "particular plant varieties cultivated, the climatic and soil conditions and the cultivation practices indigenous to northern India and Pakistan." The patent document claims that, despite its high quality, this rice has the deficiency of 'grain chalkiness.' It explains how attempts to grow the same rice varieties elsewhere (e.g. in the US) have failed, because of different climatic conditions.

The patent describes how conventional plant breeding and an apparently novel form of analysis using the 'starch index' was used to produce new rice plants that could reproduce the unique qualities of basmati rice, and could be grown in other regions lacking the distinctive climatic and soil conditions of the Punjab.

The patent originally claimed:

- a new variety of rice plant (claim 1);
- the seed of this plant (claim 12); and
- a method of selecting and breeding these rice plants (claim 18).

Other claims relate to more closely defined versions of these basic claims.

According to one report, research by the UK Government has confirmed that the RiceTec 'basmati-style' rice products are genetically distinct from South Asian basmati varieties, and are genetically closer to U.S. long-grain rice varieties.

The same company (RiceTec) has marketed its rice using the trade marks 'Texmati' and 'Jasmati.' It has also sought registration for these trade marks.

Article 15: Trade Marks

Are Texmati and Jasmati eligible as trade marks? Are they 'capable of distinguishing' rice sold by RiceTec?

Articles 22, 23 and 24: Geographical Indications

22.1: Is 'basmati' potentially a geographical indication? What would you need to find out to determine this?

22.2: If RiceTec used the word 'basmati' would it mislead the public as to the geographical origin of the rice? Would it be unfair competition within the meaning of Article 10bis of the Paris Convention?

Does the use of 'Texmati' or 'Jasmati' mislead the public as to the geographical origin of the rice, or amount to unfair competition?

23.1: Should TRIPS be amended to prevent use of 'basmati-style' for other varieties of rice, even when the consumer is not deceived as to the geographical origin of the rice?

24.6: Does 'basmati' qualify as 'the term customary in the common language as the common name' for such rice? How would you determine this?

Article 27: Patentable subject matter

27.1 Is the RiceTec rice plant and breeding/selection method:

- New?
- Inventive?
- Capable of industrial application?

27.2: Is it possible to deny patent protection to some or all of the claims of the RiceTec patent on the basis of Article 27.2?

27.3: Is it possible to deny patent protection to some or all of the claims of the RiceTec patent on the basis of any of the provisions of Article 27.3?

Articles 28 and 30: Patent rights

- What rights does this patent give to RiceTec?
- Does the patent entitle RiceTec to grow its patented rice or any basmati rice in the US or elsewhere?
- Can the patent affect anyone producing, exporting, or trading in basmati rice?:
- What exceptions to those rights should others be entitled to?
- Does this patent give the patent owner the right to grow the patented rice strain?
- Does it give the patent owner the right to describe the patented rice as 'basmati'?

Cancellation of patent rights

There has been a claim to revoke or cancel this patent, on the basis that it is not valid. On June 6, 2000, the following request for re-examination of this patent was officially published:

> 5,663,484, Reexam. No. 90/005,709, Apr. 28, 2000, Cl. 800/320.2,
>
> BASMATI RICE LINES AND GRAINS, Eugenio Sarreal, et. al., Owner of Record: Ricetec, Inc., Alvin, TX, Attorney or Agent: Pennie and Edmonds, New York, NY, Ex. Gp.: 1649, Requester: Merchant and Gould, Minneapolis, MN

In the US, the reexamination process can result in the patent being cancelled. In this example, if this move were successful, what would be the effect of cancelling the patent?

- Would it affect the right of the patent owner to produce and sell the patented rice?
- How would it affect the rights of other US rice growers who might be interested in producing this kind of rice to compete with traditional Basmati rice?
- How would it affect the interests of the traditional growers and exporters to the US market of Basmati rice?

In fact, the patent holder voluntarily withdrew a number of claims and several more were cancelled by the US Patent Office, with the consequence that the remaining claims still in force

concern only the exact varieties bred by RiceTec, and not the broader claims describing rice with certain properties such as in claim 1. This was because the broader claims could not be distinguished adequately from the documented prior art – the existing rice varieties that were available before RiceTec produced its new varieties.

Other issues:

- Does this invention make use of traditional knowledge?
- How can such traditional knowledge be recorded and documented?
- How can such traditional knowledge be protected?
- What is the scope of 'unfair competition' under TRIPS and the Paris Convention (Art. 10*bis*)

2.13 Attachments

Attachment 2.1 Extracts from Patent Documents: Use of turmeric in wound healing

Attachment 2.2 Extracts from Patent Documents: Basmati rice lines and grains

EXTRACTS FROM PATENT DOCUMENTS

United States Patent *5,401,504*
Das , et al. **March 28, 1995**

Use of turmeric in wound healing

Abstract

Method of promoting healing of a wound by administering turmeric to a patient afflicted with the wound.

Inventors: **Das; Suman K.** (Jackson, MS); **Cohly; Hari Har P.** (Jackson, MS)
Assignee: **University of Mississippi Medical Center** (Jackson, MS)

Appl. No.: **174363**
Filed: **December 28, 1993**
U.S. Class: **424/195.1**; 514/925; 514/926; 514/927; 514/928
Intern'l Class: A61K 035/78
Field of Search: 424/195.1

References Cited [Referenced By]

U.S. Patent Documents

4719111	Jan., 1988	Wilson	424/195.
5120538	Jun., 1992	Oei	424/195.
5252344	Oct., 1993	Shi	424/682.

Other References

Institute GA. 99: 218620T (1983) of JPN. 58-162520 (Ulcer Inhibitor Tablets Effective in Mice Contain Carcinogen). Soma et al GA. 116: 221612S (1992) of JPN 4-49240 (Digestive Tract Ulcers Treated with Curcuma longa (Turmeric) Extract (Lipopolysaccharides)). Kumar et al GA.119: 871K (1993) of Ind. Vet. J. 70(1):42-4 (1993). Abstracts of Charles et al Trop. Geogr. Med: 44(1-2) 178-181 Jan. 1992; Rafatullah et al J. Ethnopharmacol. 29(1): 25-34 Apr. 1990; Kutton et al Tumori 73(1): 29-31 Feb. 28, 1987; Mehra et al. Tokai J Etpharm Med 9(1): 27-31 Mar. 1984.

Primary Examiner: Rose; Shep K. *Attorney, Agent or Firm:* Wenderoth, Lind & Ponack

Claims

1. A method of promoting healing of a wound in a patient, which consists essentially of administering a wound-healing agent consisting of an effective amount of turmeric powder to said patient.

2. The method according to claim 1, wherein said turmeric is orally administered to said patient.

3. The method according to claim 1, wherein said turmeric is topically administered to said patient.

4. The method according to claim 1, wherein said turmeric is both orally and topically administered to said patient.

5. The method according to claim 1, wherein said wound is a surgical wound.

6. The method according to claim 1, wherein said wound is a body ulcer.

BACKGROUND OF THE INVENTION

The present invention relates to the use of turmeric to augment the healing process of chronic and acute wounds.

[……]

Turmeric, a yellow powder developed from the plant Curcuma longa, is commonly used as a food colorant in many Indian dishes and imparts a bitter taste. Turmeric is also used as an additive in prepared mustard.

Although it is primarily a dietary agent, turmeric has long been used in India as a traditional medicine for the treatment of various sprains and inflammatory conditions (Rao T S et al., Indian J. Med. Res., 75:574-578, 1982).

[……]

SUMMARY OF THE INVENTION

The present invention is directed to the use of turmeric to promote wound healing. The present inventors have found that the use of turmeric at the site of an injury by topical application and/or oral intake of turmeric will promote healing of wounds.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method of promoting healing of a wound in a patient, which comprises administering a wound-healing effective amount of turmeric to the patient.

The present inventors postulated that turmeric may have significant antineoplastic, antioxidant, antibacterial and anti-inflammatory properties when given orally or applied topically. In view of these facts and the availability of turmeric, the present inventors studied the wound healing properties of turmeric to provide a simple and economical solution to the problem of chronic ulcers.

[……]

Some investigators hold that there is no single factor that can address the problem of wound healing. The literature and various conferences stress the use of several growth factors for healing wounds. This multifactorial approach would result in a very high economic burden on an already strained health care system. Also, turmeric is a natural product that is readily available in the food store.

[……]

Thus, turmeric offers an alternative to conventional therapy for full-thickness wounds. Considering that turmeric is readily available and economical, this could be of particular importance to the indigent population, which suffers significant morbidity from complex wounds.

Growth factor knowledge, the use of animal models, and the body of literature on wounds per se have not conclusively addressed the serious problem of skin ulcers. One report detailed an investigation in which two factors, neem and turmeric, were used to treat scabies in a village in India. This multi-drug approach is more difficult to assess than the single factor approach being used here for humans (Charles V, Charles S X., Trop. Geogr. Med., 44:178-181, 1992). Growth factors, in particular platelet derived growth factor (PDGF) and transforming growth factor-B are potential mitogens for epithelialization as well as fibroblasts (Pierce G F et al., J. Cell Biol., 109:429-440, 1989). In contrast, in the use of turmeric there is more selectivity with respect to mitogenicity. In smooth muscle cell research, rabbit smooth muscle cells from the aorta have been shown to inhibit smooth muscle cell proliferation (Huang H-C et al., Eur. J. Pharmacol., 221:381-384, 1992).

The route of intake of a drug is also very important. The advantage of using a drug topically as well as taking it orally would be that one is addressing the problem in two ways. Turmeric has been shown to increase HDL in comparison to LDL and hence may also be used in influencing the capillary system by altering the lipid content of blood. Very little of turmeric is systemically absorbed and hence may be working as an advantage by reducing the cholesterol in the blood and hence altering the patency of the vasculature.

The need to address the problem of skin ulcers is apparent. No current animal model, single factor or drug exists (Rasmussen L H et al, Ann. Surg, 216:684-691, 1992). The literature has stressed more on carcinogenic, inflammatory metabolic modulatory or the oxidation properties of turmeric but no one has used this agent singly for wound healing. The present inventors are the first ones to use turmeric topically and orally as a single agent modality for wound healing.

The turmeric can be used in the form of a powder, such as is obtained in a food store. It can be administered orally and/or topically directly to the wound. When oral administration is employed, either alone or in combination with topical administration, turmeric is orally administered in an amount of 0.1-2.5 mg/kg of body weight. When topical administration is employed, either alone or in combination with oral administration, the amount topically administered is 0.1-1.0 gm/cm.sup.2 of wound surface. These dosage levels are daily dosages and such amounts can be administered all at once or in divided doses.

The turmeric powder can be orally ingested, for example with drinking water. The powder can also be directly administered topically to the wound.

The turmeric can be administered to mammals, including humans, to promote wound healing. Any type of wound on the outside surface of the body can be treated, for example, surgical wounds (such as incisions), ulcers, and any other injury to the body in which the skin or other tissue is broken, cut, pierced, torn, etc.

[……]

[Experimental evidence and case histories follow…]

EXTRACTS FROM PATENT DOCUMENTS

United States Patent *5,663,484*
Sarreal , et al. **September 2, 1997**

Basmati rice lines and grains

Abstract

The invention relates to novel rice lines and to plants and grains of these lines and to a method for breeding these lines. The invention also relates to a novel means for determining the cooking and starch properties of rice grains and its use in identifying desirable rice lines. Specifically, one aspect of the invention relates to novel rice lines whose plants are semi-dwarf in stature, substantially photoperiod insensitive and high yielding, and produce rice grains having characteristics similar or superior to those of good quality basmati rice. Another aspect of the invention relates to novel rice grains produced from novel rice lines. The invention provides a method for breeding these novel lines. A third aspect of the invention relates to the finding that the "starch index" (SI) of a rice grain can predict the grain's cooking and starch properties, to a method based thereon for identifying grains that can be cooked to the firmness of traditional basmati rice preparations, and to the use of this method in selecting desirable segregants in rice breeding programs.

Inventors: Sarreal; Eugenio S. (Pearland, TX); Mann; John A. (Friendswood, TX); Stroike; James Edward (League City, TX); Andrews; Robin D. (Seabrook, TX)
Assignee: RiceTec, Inc. (Alvin, TX)
Appl. No.: 272353
Filed: July 8, 1994
U.S. Class: 800/200; 800/205; 800/DIG.57; 47/58; 47/DIG.1
Intern'l Class: A01H 005/00; A01H 005/10; A01H 001/04
Field of Search: 800/200,250,DIG. 57 47/58,58.01,58.03,DIG. 1

References Cited **[Referenced By]**

U.S. Patent Documents

5208063	May., 1993	Andrews et al.	426/482.

Other References

[.....]

Claims

1. A rice plant, which plant when cultivated in North, Central or South America, or Caribbean Islands

a) has a mature height of about 80 cm to about 140 cm;

b) is substantially photoperiod insensitive; and

c) produces rice grains having

i) an average starch index of about 27 to about 35,

ii) an average 2-acetyl-1-pyrroline content of about 150 ppb to about 2,000 ppb,

iii) an average length of about 6.2 mm to about 8.0 mm, an average width of about 1.6 mm to about 1.9 mm, and an average length to width ratio of about 3.5 to about 4.5,

iv) an average of about 41% to about 67% whole grains, and

v) an average lengthwise increase of about 75% to about 150% when cooked.

[……]

11. A rice plant produced from RT1121 seed having the accession number ATCC 75940.

12. A seed produced by the rice plant of any of claims 1 to 11.

[……]

18. A method of selecting a rice plant for breeding or propagation, comprising the steps of:

a) preparing rice grains from rice seeds;

b) determining

i) the percent amylose (PA), and

ii) the alkali spreading value (ASV) of samples of said grains;

c) summing said PA and said ASV to obtain the starch index (SI) of said grains;

d) identifying a rice plant which produces grains having an average PA of about 22 to about 29, an average ASV of about 2.9 to about 7, and an average SI of about 27 to about 35;

e) selecting a seed from said plant; and

f) growing said seed into a plant.

[……]

FIELD OF INVENTION

The invention relates to novel rice lines and to plants and grains of said lines. The invention also relates to a novel method for identifying rice grains that can be cooked to a specific texture and the use of said method to select for desirable rice plants in breeding programs. Specifically, one aspect of the invention relates to novel rice lines with plants that are semi-dwarf in stature, substantially photoperiod insensitive and high yielding, and that produce rice grains having characteristics similar or superior to those of good quality basmati rice grains produced in India and Pakistan. Another aspect of the invention relates to novel rice grains produced from said novel rice lines. The third aspect of the invention relates to the finding that the likely texture and firmness of cooked rice can be predicted by the "starch index" (SI) of the grain and to the use of SI to identify desirable segregants in rice breeding programs.

2. INTRODUCTION

[……]

2.2 Basmati Rice

Although there is no single precise definition of basmati rice, it is generally accepted that good quality basmati rice has a unique combination of characteristics. Good quality basmati rice has a distinctive and pleasant aroma, long slender grains, extreme grain elongation on cooking, and a dry, fluffy texture when cooked. See Sood and Siddiq, 1980, Studies on Component Quality Attributes of Basmati Rice, Oryza Sativa, L.; Z. Pflanzenzuchtg 84:294-301. The distinctive aroma of basmati rice has been described as "popcorn" like and identified as being mostly due to the presence of 2-acetyl-1-pyrroline (2-AP). Good basmati rice typically has an average milled length to width ratio of around 4 and elongates lengthwise about 100% or so when cooked. Basmati rice, which can be cooked to a dry and fluffy texture, is traditionally preferred and a premium is paid for this quality.

[……]

2.3 Indian and Pakistan Basmati Rice

Good quality basmati rice traditionally has come from northern India and Pakistan. Some of the better known good-quality basmati varieties from India and Pakistan include Basmati 370, Type-3 (Dehradum Basmati) and Karnal Local. The superior quality of such basmati rice is well known to discriminating rice consumers. Indeed, in some countries the term "basmati rice" can be applied to only the basmati rice grown in India and Pakistan. For example, the Grain and Feed Trade Association in the United Kingdom (the largest basmati rice market in Europe and one of the largest importers of basmati rice in the world) in cooperation with the U.K. Local Authorities Coordinating Body on Trading Standards (LACOTS) has established a Code of Practice for Rice which is used by companies which operate in that market. This code allows the term basmati rice to be applied to only the long grain aromatic rice grown in India and Pakistan. Similarly, Saudi Arabia, the world's largest importer of basmati rice, has labelling regulations that permits basmati rice from only India and Pakistan and not Thailand to be marketed as basmati rice.

The basis of the distinctiveness of good quality Indian and Pakistan basmati rice remains unclear. Some believe that it is due to a unique combination of the particular plant varieties cultivated, the climatic and soil conditions and the cultivation practices indigenous to northern India and Pakistan. See Fantastic Foods.RTM. Basmati Rice Package, United States, 1994; Tilda.RTM. Basmati Rice Package, United States, 1994. In northern India and Pakistan, basmati seed are planted in nursery beds during July. In August and September, when the seedlings reach about eight inches in height, they are transplanted by hand in water flooded fields. The rice is harvested towards the end of October and in November. The plants are tall in stature (about 160 cm or more) and prone to lodging. Only modest amounts of fertilizer are used. Field yields are low at about 2,000 to 2,500 lbs per acre but the crop is economically viable since basmati rice from these regions sells in world markets for about twice the price of regular rice.

Notwithstanding the high demand for good quality Indian and Pakistan basmati rice, grain chalkiness is a notable deficiency of nearly all Indian and Pakistan basmati rice. Consumers generally prefer translucent or creamy white grains to dull, chalky grains. Chalk-like appearance on the dorsal side of the grain is known as "white belly" and in the center of the grain as "white center". Basmati rice from India and Pakistan has a higher percentage of white centered and white belly grains than American long grain rice. This apparently is varietal and environmentally related. The harvesting of basmati rice late in the year in India and Pakistan under wet and cool conditions can increase chalkiness. Aside from inferior visual appeal, chalky grains tend to break during milling. This causes an economic loss since broken grains are of a lower value. Broken grains are not desirable in basmati rice for reasons of appearance and causing stickiness in the cooked rice. Moreover, even where the grains remain intact, chalky grains tend to be soft and discolored when cooked, which is undesirable in basmati rice preparations.

Measurements of perceived good quality basmati rice from India and Pakistan show in general that the grains: (i) elongate by more than 75% during cooking, yielding whole grains with a length to width ratio 3.5, (ii) have a strong "popcorn" aroma, (iii) are somewhat chalky (white center) and generally have a low transparency, (iv) are often milled to a low degree and thus show more bran streaks, (v) vary considerably in color and chalkiness from lot to lot, and (vi) cook to a dry and fluffy texture. Good quality basmati rice from India and Pakistan also have distinctive starch properties in the way of apparent amylose contents of greater than 21%, low gelatinization temperatures and a medium to hard gel consistency.

The variable quality of Indian and Pakistani basmati rice has compelled many commercial buyers of such rice to take extensive quality assurance measures. Experienced buyers examine the paddy or brown rice, test mill the rice, examine milled rice quality; and cook a white milled

rice sample before making an overall assessment of value and price. The number of attributes to be assessed in basmati rice is greater than for any other rice product, the potential for error is significant, and the high cost of the rice increases the financial risk to a prospective purchaser. The common practice of storing or aging basmati rice for many months creates an opportunity for insect infestation, discoloration and a loss of identity as lots are often mixed together. It is allowable in the UK for basmati rice from these countries to contain a 10% admixture of other varieties and this complicates evaluations. Many rice purchasing/marketing companies require strict control of quality throughout the production chain, including knowledge of the specific variety and the use of pesticides and chemicals during production and storage. This is difficult and often impossible to determine when the rice is grown remotely from the market in the West. Importation of basmati rice into the United States has been stopped on occasions by the federal grain inspection authorities due to significant infestation and contamination problems.

2.4. Basmati Rice Production Elsewhere

Seeds of the traditional basmati rice varieties have been produced outside of India and Pakistan but not on a commercial basis. Most of these varieties are photoperiod sensitive and require a specific, short day length before they will flower. This results in the plants flowering and maturing in the fall of the year regardless of the date of planting. Such photoperiod sensitive basmati rice grown at about the same latitude in another country (e.g., about 30.degree. N in Texas in the United States) will be ready for harvest in late October or November, which is too late for a commercial crop. If planted in March (a normal planting time in Texas) the plant will add foliage until the critical day length is reached and will only then flower. Consequently, the plants become very tall and leafy, causing lodging under high winds and rainy conditions. The maturity of such Texas-grown basmati varieties can reach 200 days or more. In contrast, a typical U.S. rice variety matures and can be harvested in about 115 days after seeding and a ratoon crop may also be obtained after another 45 days. Late June or July planting of a photoperiod sensitive Indian or Pakistan basmati line gives a better plant type but the yields are low and the rice may be subject to early frosts and may not mature.

2.5. Basmati Rice Breeding Efforts

Efforts to improve the versatility or productivity of basmati rice lines have had only limited success. One prong of such efforts has been to breed rice lines that can be productively cultivated in the Western hemisphere and produce grains with some of the desired basmati grain characteristics. These efforts have yielded a number of aromatic rice types often referred to generically as "basmati type rice", including Della rice and the widely distributed Texmati.RTM. brand rice. These products have somewhat less aroma and flavor than premium basmati rice from India and Pakistan. Moreover, they typically elongate only 50% on cooking (which is about the same extent as regular long grain rice), and have cooked textures somewhat different than that of traditional good quality basmati rice.

Another prong in the improvement effort has been that of the Indian and Pakistani scientists, which is to breed higher yielding, more widely adapted basmati varieties. Their objective has been to reduce costs and to expand basmati production into other parts of the Indian subcontinent. These efforts were started in the mid-sixties with the objective of transferring the unique quality grain features of traditional basmati rice into the high yielding semi-dwarf "Green Revolution Rice Types" varieties. Such transfers are desirable in part as photoperiodism has been bred out of most of the semi-dwarf varieties. In general, the days from planting to maturity of a non-photoperiod sensitive plant do not differ much when planted at different times of the year. Thus, such plants are more adaptable to different growing regions and conditions than are photoperiod sensitive plants. Achieving this in basmati whilst maintaining all of the desired grain traits has not been accomplished. Despite decades of persistent effort, the targeted genotypes have not been achieved.

Although nearly a score of new varieties have been released between 1970 and 1992 which possessed medium slender to long slender grains with aroma, none has all of the quality traits of traditional basmati. More recently, new semi-dwarf (about 105 cm tall) basmati varieties Kasturi and Pusa Basmati-1 have been released (N. Shoba Rani, 1992, Research Efforts to Develop Scented Quality Rice--India--IRRI Newsletter). These are more promising but again they do not have all the properties of traditional basmati (Letter from Agriculture Counselor-New Delhi USDA/FAS to USA Rice Council-December 1993). Thus, even though some call the new varieties basmati rice, the new varieties more properly should be described as basmati substitute or quasi basmati rice.

The limited success in improving the versatility and productivity of basmati rice lines supports the belief in consumer, trade and scientific circles that authentic basmati rice can only be obtained from the northern regions of India and Pakistan due to the unique and complex combination of environment, soil, climate, sowing practices and the genetics of the basmati varieties. For example, a typical basmati rice package states: "Basmati rice has been grown for centuries near the foothills of the Himalayas in northern India where the soil conditions are optimal. Farmers in other parts of the world have attempted to duplicate Basmati Rice but have not been able to capture the unique qualities of the original, authentic Indian variety" (Fantastic Foods.RTM. Basmati Rice Package--United States--1994). Another package states "Tilda.RTM. Basmati rice has travelled from the foothills of the Himalayas. It has been carefully tended and harvested by hand in an area whose unique soil and climatic characteristics give the rice its exquisitely delicate texture, flavor, and aroma" (Tilda.RTM. Basmati Rice Package--United States--1994).

Scientifically, it has been reasoned that the cool growing temperatures and the late harvesting of basmati rice prevalent in northern India and Pakistan account for the low gelatinization temperature and perhaps the high chalkiness of authentic basmati rice and that these properties are essential to the particular basmati cooked grain characteristics. It has also been reasoned that these cool conditions are responsible for the high level of aroma and flavor associated with the presence of 2-acetyl-1-pyrroline since this compound is volatile. On this basis then it would not be possible to achieve the desirable basmati grain properties and qualities by breeding them into a semi-dwarf plant which would mature quickly and grow in a hotter climate, even if the complex trait breeding process could be accomplished. See Soomo and McLean, 1992, High Yielding Rice Varieties in West Pakistan, International Rice Research Institute.

2.6. Breeding Challenges

Speculations aside, the challenges in developing higher yielding, widely adapted and higher quality basmati varieties are formidable. The odds against the successful combining of basmati grain traits with desirable plant traits found in advanced semi-dwarf varieties by plant breeding is daunting. Basmati grains have four to five characteristic traits, i.e., aroma, elongated grain shape (grain length and width), extreme elongation of the cooked grain and dry, fluffy cooked texture. Of these, aroma is perhaps the most simply inherited. Most literature suggests either one or two genes (and possibly an additional repressor gene) as encoding the functions giving rise to aroma. (Berner and Hoff, 1986, Inheritance of Scent in American Long Grain Rice, Crop Science 26:876-878; Dong et al., 1992, Genetic studies of aroma in the elite cytoplasmic male sterile (CMS) aromatic japonica line, Shanghai A, International Rice Research Institute Newsletter 17:5). The quantitative aspect of aroma, however, has not been described, but may well be controlled by several more genes. The genetics of the other basmati grain traits is even less well understood. However, each of these other traits is likely encoded by more genes than those determining aroma. Even assuming an average of only 7 genes in encoding each of the other three basmati grain traits, then the ideal combination of all basmati-specific grain traits will occur with a frequency of less than 1:900. In comparison, it is often assumed that at least one hundred genes are involved in the quantitative aspects of agronomically important plant

traits such as seed yield, milling yield, plant height, maturity, tillering, panicle shape and size, disease resistance and photoperiod sensitivity. Together, the frequency of the "best combination" of desirable basmati grain and semi-dwarf plant traits is likely to be less than 1:16,000.

Moreover, many of these grain and plant traits are highly responsive to the environment. For example, milling yields might vary from 20% to 65%, grain starch properties, which control rice cooking behavior and cooked rice texture, might also vary widely, and yield can vary from nil to 10,000 kilograms/hectare, all depending on the environment. This highly complicates the chances of finding the 1 variant in 16,000. Moreover, as the genes encoding these traits do not assort at random, the odds are further diminished. For example, in basmati rice good grain traits appear to be strongly associated with poor plant types. Such unfavorable linkages further diminish the odds of success. Thus, it is unclear that, even under favorable circumstances, classical plant breeding can produce a rice plant that combine desirable basmati grain traits with the superior plant traits of semi-dwarf rice varieties.

The difficulties in breeding higher yielding, widely adapted and higher quality basmati varieties is further compounded by the fact that the desirable dry, fluffy cooked texture of good quality basmati rice is a complicated trait and a difficult one to assay. Although the trait is genetically determined, its manifestation in cooked rice is controlled by the way the rice is processed and cooked. Rice which is milled to remove the bran but leave more of the aleurone and sub-aleurone layers in place cooks drier and fluffier than rice which has been milled to a higher degree. See Osborne et al., 1993, The Authentication of Basmati Rice Using Near Infrared Spectroscopy, Near Infrared Spectroscopy 1:77-83; Flour Milling and Baking Research Association (FMBRA) report for United Kingdom (UK) Ministry of Agriculture and Fisheries year ending March 1993. Aging of the rice, for months or years, also enhances this trait. The extent of milling and aging, however, also changes the way the rice cooks. Specifically, both aging and reduced milling increases the amount of water and the time needed to cook the rice to the desired optimal texture. Thus, assaying this trait in cooked rice must consider the interplay of these different factors and the results obtained therefrom must be interpreted accordingly.

[.....]

3. SUMMARY OF THE INVENTION

One aspect of the instant invention relates to novel rice lines and to the plants and grains of said lines. Another aspect of the invention provides for a novel method of identifying rice grains that can be cooked to the dry and fluffy texture typically found in good quality basmati rice preparations and the use of said method to select desired lines in rice breeding programs. In particular, the present invention provides novel rice lines, whose plants are semi-dwarf in stature, substantially photoperiod insensitive, high yielding and produce rice grains comprising grain characteristics and qualities similar or superior to those of good quality basmati rice grains produced in India and Pakistan. The invention also relates to the discovery that the likely texture of cooked rice can be predicted by measuring a grain's "starch index" (SI), which is the sum of its percent amylose (PA) and alkali spreading value (ASV), and the use of SI in selecting desirable segregants in rice breeding programs.

The present invention makes possible the production of high quality, higher yielding, basmati rice worldwide. It is based, among other things, on the surprising discovery that certain basmati plant and grain characteristics and aspects of the growing environment for traditional basmati rice lines are not critical to perceived basmati product quality and that classical plant breeding methods can be used to combine, in novel rice lines, the desirable grain traits of basmati varieties with the desirable plant and grain traits of semi-dwarf, long grain varieties. The invention is also based, in part, on the discovery that the texture of cooked grains is related to the uncooked grains' SI. Seeds exhibiting a PA or ASV which might previously be rejected on a

separate basis are found to give acceptable rice cooking behavior and texture when the SI lies within certain limits. In this way the effectiveness of the breeding process is improved. The SI can be easily and conveniently determined with a very small amount of sample, the discovery enables effective selection and thus breeding of the texture trait that heretofore has been an obstacle in the breeding of basmati grain traits. The invention is illustrated by several examples of novel rice lines whose plants embodies the desired combination of plant and grain traits. These new lines evidence the reproducibility and broad applicability of the disclosed teachings in developing the claimed novel rice lines.

[……]

5. DETAILED DESCRIPTION OF THE INVENTION

The instant invention provides novel rice lines and the plants and grains of said lines. The rice lines of the invention combine desirable grain traits of basmati rice with desirable plant traits of semi-dwarf, long grain rice. In particular, the combined traits comprise the basmati grain traits of "popcorn" aroma, long slender grain shape, extreme grain elongation on cooking, and dry, fluffy (or firm) texture of the cooked grain and the semi-dwarf, long grain plant traits of short stature, photoperiod insensitivity, high grain yield, and disease tolerance. In addition to the desired basmati grain traits, the grains of the invention have superior characteristics of high whole grain index, low chalkiness and low burst index. The invention also provide a novel, convenient method for screening rice grains that can be cooked to the firmness of good quality basmati rice preparations and the use of said method in rice breeding program. In particular, the novel method is based on the discovery that the likely firmness and texture of cooked rice grain can be predicted by its "starch index" (SI), which consists of the sum of grain's percent amylose (PA) (excluding the effect of aging) and alkali spreading value (ASV).

The novel rice lines of the invention may be produced by classical plant breeding using basmati and semi-dwarf, long grain parents that have the desired grain and plant traits, respectively, and using selection schemes comprising the novel method for screening of the cooked grain texture trait. The invention is illustrated by examples that 1) compare plant and grain characteristics of basmati rice and long grain rice, 2) demonstrate the relationship between the starch index and cooked grain firmness, 3) account the breeding of several novel rice lines of the invention, and 4) examine the plant and grain characteristic of the a novel rice line of the instant invention.

The various embodiments of the claimed invention described herein are by the way of illustration and are not meant to limit the invention. Specifically, the preferred embodiments describe a number of features which an artisan may recognize as not being absolutely essential, but clearly advantageous. They include the parental lines and the selection scheme used in the disclosed breeding program. The utilities of the disclosed breeding and selection scheme are broadly applicable to crosses among a wide range of parental lines and to many permutations of the disclosed selection scheme. Given the instant teachings, one skilled in the art would know the appropriate equivalent parental lines, approaches and methods needed to practice the present invention. Further, many of the plant breeding methods and rice grain assays which could be used in part to practice the instant invention are variety- and grain-independent and are well known to those skilled in the art. See Briggs, F. N. and Knowles, P. F., Introduction to Plant Breeding, 1967, Reinhold Publishing Corporation; Allard, R. W., Principles of Plant Breeding, 1966, John Wiley and Sons, Inc.

5.1. Novel Rice Lines

A rice line of the invention is genetically substantially homozygous and thus can be reproduced by planting seeds of the line, growing the resulting plants under self-pollinating or sib-pollinating conditions, and harvesting the resultant seeds, using techniques know in plant breeding. The invented lines show phenotypic uniformity and stability within the limits for all traits described herein. The plant, seed, and grain characteristics described herein for the

invented lines are the typical values for the invented lines cultivated in Puerto Rico or Alvin, Tex., or Newport, Ark., or Dewitt, Ark. or Belle Glade, Fla.

According to the invention, a rice line of the invention is semi-dwarf in stature. The mature plants of an invented line have an average height of less than about 150 cm, or preferably an average height of less than 115 cm, or more preferably an average height of less than 95 cm. In one embodiment, the mature rice plants have an average height of 115 cm. In another embodiment, the mature rice plants have an average height of 120 cm.

A rice line of the invention also is substantially photoperiod insensitive. The rice plants of an invented line flower at approximately the same age when planted any time within a relatively wide window of "planting season". More particularly, the plants of an invented line flower approximately 90 to 110 days and mature approximately 110 to 130 days after planting when planted in the northern hemisphere any time from the beginning of March to the end of June. In a particular embodiment, the rice plants flower approximately 95 days and mature approximately 124 days after planting. In another embodiment, the rice plants flower approximately 98 days and mature approximately 128 days after planting.

A rice line of the invention moreover is high yielding. When cultivated using standard North American production practices, the rice plants of an invented line produce an average dried rough rice grain yield of at least about 3,700 lbs/acre, or preferably at least about 5,000 lbs/acre, or more preferably at least about 6,000 lbs/acre. In one embodiment, the rice plants produce an average seed yield of about 5,300 lbs/acre. In another embodiment, the rice plants produce an average seed yield of about 5,400 lbs/acre.

A rice line of the invention further is disease tolerant. The rice plants of an invented line are moderately susceptible to blast and sheath blight, or preferably moderately tolerant to blast (Pyricularia oryzae), sheath blight (Rhizoctonia oryzae) and straighthead, or more preferably resistant to blast, sheath blight and straighthead. In particular embodiments, the rice plants of two invented lines are moderately tolerant to blast and sheath blight.

A rice line of the invention furthermore is high tillering. The rice plants of an invented line produce an average of at least 2 to 3 tillers per plant, or preferably an average of 4 tillers per plant, or more preferably an average of 5 or more tillers per plant. In particular embodiments, the rice plants of two invented lines produce an average of 4 tillers per plant when plant stands are about 20-30 plants per square foot.

A rice line of the invention further produce rough rice grains (seeds) that can be processed (i.e., dried, de-hulled and milled) to yield a high percentage by weight of whole grain rice (WG). The rice plants of an invented line produce seeds that can be processed to yield grains containing an average of at least 40% WG, or preferably an average of at least 52% WG, or more preferably an average of at least 62% WG. In a particular embodiment, the rice plants produce seeds that can be processed to yield grains containing an average of about 50% WG. In another embodiment, the rice plants produce seeds that can be processed to yield grains containing an average of about 45% WG.

A rice line of the invention furthermore produces seeds that can be processed to grains with the characteristics described in section 5.2.

5.2. Rice Grains of the Invention

A rice line of the invention produce seeds which can be processed to grains comprising desirable characteristics traditionally identified with those of good quality basmati rice grains produced in the Indian subcontinent. Such grain characteristics include, but are not limited to, long thin grain shape, distinctively pleasing taste and aroma, extreme elongation of the cooked grain, and the dry and fluffy (or firm) texture of the cooked rice.

The various grain traits of the invented line described herein are those of de-hulled and milled grain. The de-hulling and milling of seeds to grains may be by any means known in the art. The

grains of the invention are milled to between about 60 SMD and about 100 SMD, or their equivalents (see U.S. Pat. No. 5,208,063) when tested as white rice.

According to the instant invention, the rice grains of an invented line have an average milled grain length of at least about 6.65 mm, width of less than about 1.9 mm, and length/width (l/w) ratio of at least about 3.5. The rice grains of an invented line preferably have an average milled grain length of at least about 7.0 mm, width of less than about 1.75 mm, and l/w ratio of at least about 4.0. The rice grains of an invented line more preferably have an average milled grain length of at least about 7.3 mm, width of less than about 1.7 mm, and l/w ratio of at least about 4.3. In a particular embodiment, the rice grains have an average milled grain length of about 6.75 mm, width of about 1.85 mm, and l/w ratio of about 3.65. In another embodiment, the rice grains of invented line have an average milled grain length of about 7.26 mm, width of about 1.85 mm, and l/w ratio of about 3.92.

The rice grains of an invented line also have an average 2-acetyl-1-pyrroline content of at least about 150 parts per billion (ppb), or preferably at least about 400 ppb, or more preferably at least 800 ppb. In one embodiment, the rice grains have an average 2-acetyl-1-pyrroline content of about 400 ppb. In another embodiment, the rice grains have an average 2-acetyl-1-pyrroline content of about 150 ppb.

Moreover, rice grains of an invented line when cooked elongate lengthwise an average of at least 75%, or preferably 100%, or more preferably 120% over the uncooked grains. In a specific embodiment, the cooked rice grains of an invented line elongate an average of 90% over the uncooked grains. In another embodiment, the cooked rice grains of an invented line elongate an average of 75% over the uncooked grains.

The rice grains of the invented lines moreover have cooked grain texture and firmness comparable to that of good quality basmati rice preparations when cooked in the same manner. As described infra (see section 7.0.), the cooked grain firmness is related to Starch Index and can be so measured. Accordingly, the rice grains of an invented line have an average SI of at least about 27 with the SI consisting of an average percent amylose (PA) of at least 20 to 24 and an average alkali spreading value (ASV) of at least about 2.9 to about 7. The rice grains of an invented line preferably have an average SI of at least 30 with the SI consisting of an average PA of at least 23 to 27 and an average ASV of at least about 2.9 to about 7. The rice grains of an invented line more preferably have an average SI of at least 33 with the SI consisting of an average PA of at least 26 to 30 and an average ASV of at least about 2.9 to about 7. In an embodiment, the rice grains have an average SI of about 29 with the SI consisting of an average PA of about 24.5 and an average ASV of about 4.5. In another embodiment, the rice grains have an average SI of about 29 with the SI consisting of an average PA of about 26.2 and an average ASV of about 2.9.

The rice grains of an invented line when cooked also have an average burst index of less than about 4, or preferably less than about 3, or more preferably about 1. In a specific embodiment, the rice grains when cooked have an average burst index of about 2. In another embodiment, the rice grains when cooked have an average burst index of about 3.

The rice grains of the invented line further have low contents of chalked grains, a desired grain quality typically not found in premium basmati rice from India or Pakistan. Accordingly, rice grains of an invented line additionally have an average chalked grain content of less than 40%, or preferably less than 15%. In a specific embodiment, the rice grains have an average chalked grain content of about 8%. In another embodiment, the rice grains have an average chalked grain content of about 7%.

5.3. Breeding Novel Rice Lines

A novel rice line of the instant invention may be produced by plant breeding. Single, double, three-way and multi-line crosses involving many combinations of basmati and semi-dwarf,

long-grain parent lines can be used to produce the rice lines of the invention. The novel rice lines of the invention may be bred from such crosses by repeated selection and propagation of seeds from segregants that show improvements over the preceding generation in one or more of the desired grain or plant traits (see sections 5.1. and 5.2.). Any selection and propagation method or scheme known in the art may be used. Useful methods range from single seed descent to bulk selection. Preferred methods such as modified bulk selection or pedigreed breeding should attain maximum differentiation of plant and grain types in early screening (i.e., generations), or large enough populations in bulk advance such that the extremely rare variants are likely to be retained in the breeding population.

5.3.1. Source Material

A rice line of the invention may be selected from a population pool produced by crossing a basmati line that has many or most of the desired basmati grain characteristics (e.g., strong 2-AP aroma, long slender grain shape, extreme elongation on cooking, and a firmed texture of the cooked grain (i.e., SI, PA and ASV)) with a semi-dwarf, long-grain line that has many or most of the desired plant characteristics (e.g., short stature, photoperiod insensitivity, high seed yield, disease tolerance, early maturity and moderate to high tillering). A preferred basmati parent is any that has all the desired grain traits described in section 5.2. A more preferred basmati parent is one that has all the desired grain traits in the preferred or more preferred ranges described in section 5.2. A most preferred basmati parent is one that additionally has one or more of the desired plant traits described in section 5.1. Similarly, a preferred semi-dwarf, long grain parent is any that has all the desired plant traits described in section 5.1. A more preferred semi-dwarf, long grain parent is one that has all the desired plant traits in the preferred or more preferred ranges described in section 5.1. A most preferred semi-dwarf, long grain parent is one that additionally has one of more of the desired grain traits described in section 5.2 or that does not sun check at maturity, thus increasing whole grain milling yields.

Accordingly, a basmati line including but not limited to any of those shown in Table 1 may be used as the basmati parent, and a semi-dwarf, long grain variety including but not limited to any of those shown in Table 2 may be used as the semi-dwarf, long grain parent. A preferred basmati parent may be Bas122 (PI385418), Bas433 (PI385455) or (PI392153). In a specific embodiment, Bas433 (PI385455) is used as the basmati parent. In another embodiment, Bas397 (PI385452) is used as the basmati parent. In a specific embodiment, CB801 is used as the semi-dwarf long grain parent in the first cross and CB801E is used as the semi-dwarf, long grain parent in the subsequent top-cross. In another embodiment, GP1130 is used as the semi-dwarf, long grain parent in the first cross and LEAH is used as the semi-dwarf, long grain parent in the subsequent top-cross.

[Further extensive description follows in the original patent document]

FOREIGN AFFAIRS AND TRADE

AUSTRALIA

AusAID the Australian Government's overseas aid program

Module Three

Reading a Biotechnology Patent and the Patent Process

Intellectual Property and Biotechnology
A Training Handbook

Contents: Module Three

3.1 Objectives for Module Three

By the end of this Module you should have an understanding of:

- the structure and information provided by a patent document including:
  - the cover page
  - the specification, and
  - the claims
- interpreting a patent document
- how to read a patent document from the different perspectives of researchers, lawyers and patent offices
- the steps in the grant of a patent, including:
  - international applications under the PCT
  - the national phase, and
- the role of a patent office.

3.2 Structure of a Patent Document

The basic patent document is a patent specification, which is submitted to the patent office in support of an application to gain a patent right. This document has a range of functions:

- it defines the scope of the invention claimed, and thus determines the legal scope of the patent right;
- it describes the nature of the invention, including instructing the reader how to carry out the invention; and
- it gives details of the inventor, the patent owner and other legal information.

It often lists references to other documents, such as journal publications and other patent documents, which have been found to be relevant in the course of searches and examination on the patent's subject matter. The patent specification therefore has many potential uses:

- it creates and sets the limits to a legally enforceable right, comparable to a title deed for land, which can be sold, licensed and otherwise transferred to another owner;
- it serves as a brief text book or an instrument of technology transfer, teaching the reader about a specific form of new technology and contributing to publicly available knowledge;
- it can serve as an advertisement for potential licensing or research partners; and
- it can provide information about technological trends in various sectors, or the business or technological strategy of individual enterprises.

How you read, interpret and use a patent document will depend on which of these multiple uses you need patent information for. Collections of patent documents are available in a number of patent information databases. You can make use of patent information to:

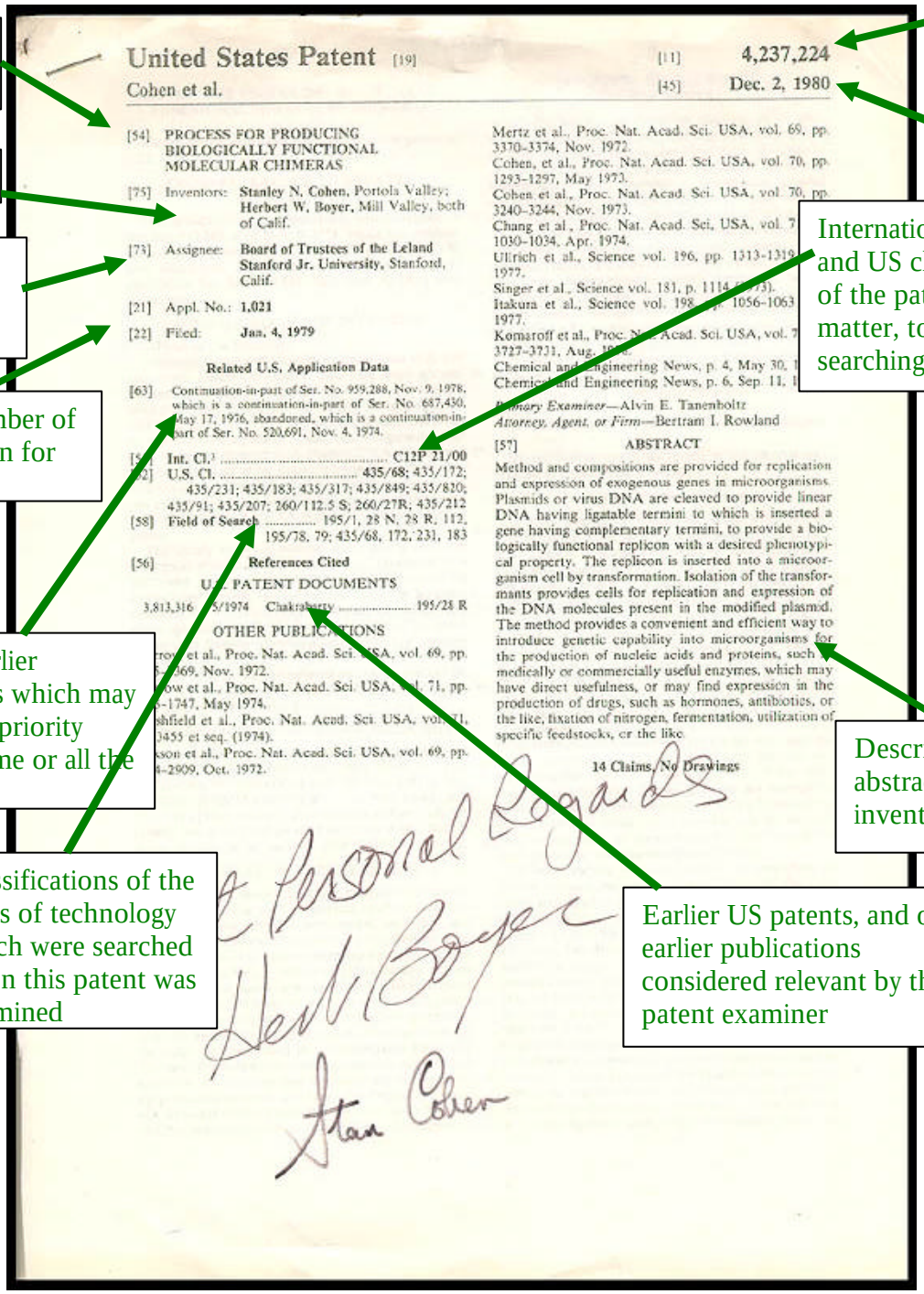
- see whether your own invention might be eligible for a patent;
- see whether someone else has already done research in an area that interests you;
- learn about the current state of the art in a field of technology that interests you;
- see whether your commercial plans might conflict with someone's existing or potential patent rights;
- gain access to applied technologies that might be available either for licensing or purchase (when the patent is in force), or available freely (when the patent is not in force in the country concerned); and
- monitor the research and commercial directions of others in the field of technology you are interested in.

Originally, anyone wanting to use patent information had to look, page by page, at copies of the original patent specification in paper form. This was very laborious and time-consuming, and it was very difficult to gain access to the information – one had to visit one of a small number of specialised patent collections. With the increasing availability of patent information on-line, this data is now much more accessible and can be virtually cost-free. It has always been an obligation on the patent holder to make the details of the invention available to the public in a form that enables a skilled person to carry out the invention. In the past, the cost and difficulty of access to information meant that its benefits were not widely shared. Recent advances in information technology now mean that this legal requirement is increasingly a practical reality around the world. Much valuable patent information is now available free of charge for anyone with an internet connection.

Please see ***Module Four*** for details of how to search patent information. This will give you further assistance on reading and interpreting patent information.

The front page of a US patent document

This is the front page of a patent issued to Herbert Boyer and Stan Cohen for their breakthrough in genetic engineering (described in Module Two).



United States Patent [19]
Cohen et al.

[11] 4,237,224
[45] Dec. 2, 1980

[54] PROCESS FOR PRODUCING BIOLOGICALLY FUNCTIONAL MOLECULAR CHIMERAS

[75] Inventors: Stanley N. Cohen, Portola Valley; Herbert W. Boyer, Mill Valley, both of Calif.

[73] Assignee: Board of Trustees of the Leland Stanford Jr. University, Stanford, Calif.

[21] Appl. No.: 1,021

[22] Filed: Jan. 4, 1979

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 959,288, Nov. 9, 1978, which is a continuation-in-part of Ser. No. 687,430, May 17, 1976, abandoned, which is a continuation-in-part of Ser. No. 520,691, Nov. 4, 1974.

[51] Int. Cl.³ C12P 21/00
[52] U.S. Cl. ..... 435/68; 435/172; 435/231; 435/183; 435/317; 435/849; 435/820; 435/91; 435/207; 260/112.5 S; 260/27R; 435/212
[58] Field of Search ..... 195/1, 28 N, 28 R, 112, 195/78, 79; 435/68, 172, 231, 183

[56] References Cited
U.S. PATENT DOCUMENTS
3,813,316 5/1974 Chakrabarty ..... 195/28 R
OTHER PUBLICATIONS
...et al., Proc. Nat. Acad. Sci. USA, vol. 69, pp. ...369, Nov. 1972.
...ow et al., Proc. Nat. Acad. Sci. USA, ...71, pp. ...1747, May 1974.
...shfield et al., Proc. Nat. Acad. Sci. USA, vol. ...1, ...3455 et seq. (1974).
...son et al., Proc. Nat. Acad. Sci. USA, vol. 69, pp. ...2909, Oct. 1972.
Mertz et al., Proc. Nat. Acad. Sci. USA, vol. 69, pp. 3370-3374, Nov. 1972.
Cohen, et al., Proc. Nat. Acad. Sci. USA, vol. 70, pp. 1293-1297, May 1973.
Cohen et al., Proc. Nat. Acad. Sci. USA, vol. 70, pp. 3240-3244, Nov. 1973.
Chang et al., Proc. Nat. Acad. Sci. USA, vol. 7... 1030-1034, Apr. 1974.
Ullrich et al., Science vol. 196, pp. 1313-1319, 1977.
Singer et al., Science vol. 181, p. 1114 (...73).
Itakura et al., Science vol. 198, ...p. 1056-1063 1977.
Komaroff et al., Proc. N... Acad. Sci. USA, vol. 7... 3727-3731, Aug. 1...
Chemical and Engineering News, p. 4, May 30, 1...
Chemical and Engineering News, p. 6, Sep. 11, 1...

...mary Examiner—Alvin E. Tanenholtz
Attorney, Agent, or Firm—Bertram I. Rowland

[57] ABSTRACT

Method and compositions are provided for replication and expression of exogenous genes in microorganisms. Plasmids or virus DNA are cleaved to provide linear DNA having ligatable termini to which is inserted a gene having complementary termini, to provide a biologically functional replicon with a desired phenotypical property. The replicon is inserted into a microorganism cell by transformation. Isolation of the transformants provides cells for replication and expression of the DNA molecules present in the modified plasmid. The method provides a convenient and efficient way to introduce genetic capability into microorganisms for the production of nucleic acids and proteins, such ... medically or commercially useful enzymes, which may have direct usefulness, or may find expression in the production of drugs, such as hormones, antibiotics, or the like, fixation of nitrogen, fermentation, utilization of specific feedstocks, or the like.

14 Claims, No Drawings

Title of the invention

Patent number

Date of issue

Inventors

Assignee (owner of the patent right)

International (IPC) and US classifications of the patent's subject matter, to assist in searching

Date and number of the application for this patent

Data on earlier applications which may give earlier priority dates to some or all the claims

Descriptive abstract of the invention

Classifications of the areas of technology which were searched when this patent was examined

Earlier US patents, and other earlier publications considered relevant by the patent examiner

In this format, the front page does not give the details of the claim, but provides information about the claimed invention in the form of a descriptive abstract. The subject matter of the claims is generally covered in the abstract, but the abstract does not have the same legal effect as the claims themselves. Further pages include a description of the invention, with an account of the background to the invention, including relevant prior art (pre-existing technology), and a detailed description of the best way known of putting the invention into practice.

Elements of a patent document

There are three key sections of a patent document:

- the cover page, including factual information concerning the inventor, the applicant, and other details of the application, its publication and its status, as well as an abstract summarising the disclosed invention (this is also called the 'front page' or the 'first page,' and this kind of information is often called the 'bibliographic' information);
- the specification/disclosure, which can include drawings and figures, explaining the technological background to the invention, and explaining how to put the invention into effect; and
- the claim or claims that define the legal scope of the invention.

With the increasing use of on-line patent databases, you might see the same information in different formats and different structures, but each full patent document you encounter should contain all of this information in some form. Some patent databases will have a subset of this information – in particular, they might just give the 'bibliographic' information that is contained on the cover page or front page – but the full patent specification always contains detailed technical description and the legal claims. As has been noted various times throughout this Handbook, patent law varies in different countries. Patent documents are also different in different countries, and of course are published in different languages. However, the key parts of a patent document are similar and easy to identify.

Reading patent documents: international data codes

To facilitate the sharing of information using the patent system, an international two-digit code is administered by WIPO, known as the INID code. "INID" is an acronym for "Internationally agreed Numbers for the Identification of (bibliographic) Data." These codes are used around the world and will appear on most published patent documents you will come across. For example, you will see each of the following codes next to the relevant information on the Cohen Bayer patent document above:

(11) Number of the patent or patent document
(21) Number(s) assigned to the application(s);
(22) Date(s) of filing the application(s);
(45) Date of making available to the public by printing or similar process of a patent document on which grant has taken place on or before the said date;
(51) International Patent Classification; (52) Domestic or national classification;
(54) Title of the invention;
(56) List of prior art documents, if separate from descriptive text;
(57) Abstract or claim; (58) Field of search;
(61) Related by addition to earlier application or grant <country> <number> <date>;
(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application <country> <number> <date>;
(71) Applicant(s), including indications in square brackets of [State of nationality/State of residence];
(72) Inventor(s); (74) Agent(s)/Common representative;
(75) Inventor(s)/Applicant(s) (for US only), including indications in square brackets of [State of nationality/State of residence].

Are you looking at an application or a granted patent?

In working with patent documents, you will come across patent documents at various stages of processing. A patent application will normally be published 18 months after the first priority date (this was not the case in the US until very recently). In some national patent systems (which allow for other parties to oppose the application before it is granted), the application is published in the form it is accepted by the patent office, to be subject to public scrutiny and possible opposition. Finally, the granted patent is separately published, particularly if it is different from the earlier published application. It is important to check the status of any document you are looking at – many patents are granted in a form different to the original application (the claims especially are likely to be amended in response to an examiner's objections). It is also important to check for any related patents – even if an application has been abandoned, some of its subject matter could be contained in a related patent.

One simple way of checking the status of an application is to look at the document code - a simple code that indicates what kind of document you are looking at. These codes are applied according to a widely accepted WIPO standard

(ST.16, available at http://www.wipo.int/scit/en).

The general format for a patent documentation number is:

Country code - Number - Document kind code

The country code is the universal two-letter code (e.g. ID for Indonesia, MY for Malaysia, MX for Mexico, AU for Australia, JP for Japan). Two specific codes you might encounter are 'EP' for the European Patent Office, and WO for PCT international applications published by WIPO.

The code for the document kind is A, B or C, in order of publication. Codes such as A1, A2 etc. give further details within these general categories. The following examples illustrate how these codes are applied in different patent systems: you will see that despite some variations, the basic principle applies that A, B and C are used for successive forms of publication.

In the Australian patent system:

AU-A	Published patent applications that has not yet been examined by the patent office, and has not been accepted.
AU-B	Patent applications that have been accepted by the patent office (and possibly amended since the AU-A publication), and are published for public scrutiny and possible opposition.
AU-C	Patent applications that have been accepted but were subsequently amended (for example, due to an error or an opposition), and therefore needed to be republished.

In the Chinese patent system:

CN A	An unexamined application open to public inspection
CN B	An examined application open to public inspection
CN C	A granted patent

In the European Patent office,

EP A1	Publication of application with search report
EP A2	Publication of application without search report
EP A3	Publication of search report
EP A4	Supplementary search report
EP A8	Corrected title page of an EP-A document
EP A9	Complete reprint of an EP-A document
EP B1	Patent
EP B2	Patent after modification
EP B8	Corrected front pages of an EP-B document
EP B9	Complete reprint of an EP-B document

In the WIPO (PCT) system:

WO A1	Publication of the international application with international search report
WO A2	Publication of the international application without international search report
WO A3	Subsequent publication of the international search report
WO B1	Publication of amended claims
WO B8	Second modification of the first page
WO B9	Correction of a complete corrected document
WO C1	Modified first page
WO C2	Complete corrected document

You will recall from *Module One* that the PCT system does not produce granted patents – the only documents it publishes are international applications prior to the commencement of the national phase in designated countries (see the full description of this process later in this Module).

In the US, the system was recently changed due to the new procedure of publishing patent applications before they are issued as granted patents. The following codes apply to US patent documents:

Document Type	Before Jan. 2, 2001	After Jan. 2, 2001
Issued patent (no pre-grant publication)	5,123,456	US 6,654,321 B1
Issued patent (with pre-grant publication)	NA	US 6,654,322 B2
Application (first publication)	NA	US 2001/0001111 A1
Second or subsequent republication of an application	NA	A2 US 2001/0002222 A2
Correction of a published application	NA	US 2001/0003333 A9

US005626882A

United States Patent [19]

Marrone et al.

[11] Patent Number: 5,626,882

[45] Date of Patent: May 6, 1997

[54] METHOD OF USING EMU OIL AS AN INSECT REPELLENT

[75] Inventors: **Pamela G. Marrone**; **Stephen A. Judd**, both of Davis, Calif.

[73] Assignees: **AgraQuest, Inc.**; **R.E. Zoogen**, both of Davis, Calif.

[21] Appl. No.: **616,708**

[22] Filed: **Mar. 15, 1996**

[51] **Int. Cl.**[6] **A61K 35/12**

[52] **U.S. Cl.** **424/522**; 424/DIG. 10

[58] **Field of Search** 424/522, 520, 424/DIG. 10

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,208,209	5/1993	Otsuji et al.	503/221
5,346,922	9/1994	Baldock et al.	514/703

OTHER PUBLICATIONS

Wantanabe et al., "Rotundial, a new natural mosquito repellent from the leaves of *Virex rotundifolia*" *Biotech Biochem.* (1995) 59(10):1979–1980.

Wantanabe et al., "New mosquito repellent from *Eucalyptus camaldulensis*" *J. Agric. Food Chem.* (1993) 41:2164–2166.

Sharma et al., "Mosquito repellent action of Neem" *Azadirachta indica oil J. Am. Mosquito Control Assn.* (1993) 9(3):359–360.

Primary Examiner—Raymond Henley, III
Attorney, Agent, or Firm—Morrison & Foerster

[57] **ABSTRACT**

This invention provides a method for repelling biting insects such as mosquitoes by topically applying emu oil to the skin.

1 Claim, No Drawings

US patent for a method of using emu oil as an insect repellent

The discussion below draws on this US patent document as an illustrative example in describing the three key parts of a patent.

This front page of the patent document includes:

- a brief abstract describing the invention, which is very close in this case to the patent claim
- references to two earlier US patent documents which were cited by the examiner in the course of examining the invention
- references to three journal publications cited by the examiner
- details of the inventor, assignee (owner), examiners and legal representative
- the number of the granted patent, and the number of the original application
- the filing date and publication date
- the relevant technological classes in the US and International classification systems

The two following pages of this document include the background to the invention, a description of the invention and preferred embodiment, and further descriptive material as well as the claim defining the patent right. This material is quoted in the following sections of this Module.

Front page

The cover page sets out administrative details of the patent (the 'bibliographic' details). These details include the title of the invention, the names of the inventor or inventors, the name of the owner of the patent (assignee or patentee), relevant dates, related patent document numbers and other key events during the patent process. In US patent documents, the cover page also includes information of the documents cited during examination. Other important information about the patent – for example, the fact that it may have expired, or it may have been cancelled or transferred to another owner – won't normally be found on the patent document itself, and you would need to get that information separately.

Patent number and title of the patent

The first thing to observe is that this is a patent document ('United States Patent') – this might seem trivial or obvious, but as we have noted it can be vital to tell between a patent *application* and an actual granted patent. The date of a US patent is at the right hand side of the top of the cover page of a patent document, under the number of the patent. For example, you can see that the number of the emu oil patent is US patent 5 626 882 and the date of issue is May 6, 1997. The title of the patent is given as "Method of using emu oil as an insect repellent." The title is for reference only, and does not determine the scope of the claimed invention.

Abstract

The abstract is a short description of the invention, which is written by the applicant. It is intended to give a more detailed guide as to the main features of the technical disclosure, unlike the title, which provides a more general description. The abstract is not referred to when the patent claims (and therefore the scope of the legal right under the patent) are being interpreted – it is purely to inform the reader, and to assist in searching. Nonetheless, the abstract often overlaps with the language used in the claims and in the detailed description of the invention in the patent document. The abstract for the emu oil example patent is simply, "This invention provides a method for repelling insects such as mosquitoes by topically applying emu oil to the skin." The abstract is often longer and more detailed – see, for example, the Cohen Boyer patent above.

Names of inventors and assignee or patentee

The names of the inventors are at the top left-hand corner of the cover page. In our example, the inventors are listed as "*Marrone et al*" with the full names of the two inventors given lower down, together with the assignees or owners of the patent (in this case, the patent right is owned jointly by two separate companies). *Modules One* and *Two* discussed how the inventor and the patentee may not be the same person. Even where this is the case, it is essential for a patent to name the inventor or team of inventors who contributed to the claimed invention – this is a legal requirement under the Paris Convention and TRIPS.

The people or organisation which owns the rights in the invention are variously known as the patentees, the patent right holders, or assignees (when the patent application is still being processed, they are of course known as the applicants). This can be because the inventor was an employee at the time they made the invention and their employment contract provided that their employer owns any rights over the invention. Alternatively the assignee might be different to the inventor because the inventor has sold the rights. This can be different in different countries – the same inventor can sell her patent rights in Malaysia to one company and her rights in the Philippines to another company, and keep them in her own name in Thailand. Regardless of who the owner is, a patent can be held to be invalid if does not provide the names of the actual inventors.

Application number and filing date

The application number and the filing date are under the names of the inventors and assignees. For example, in the emu oil patent the application number is 616 708. You will note that the application number is a different number to the actual patent number. The date of filing is

March 15, 1996. This is the date the application was lodged in the US Patent and Trademark Office. The patent term is calculated from this date – normally, in line with TRIPS provisions, the term is at least 20 years from the filing date.

Priority date

The patent document should also list a priority date. This can either be derived from a patent application filed in another country, or from an earlier application in the same country. For example, if you file a patent application in the Philippines on January 17, 1999, you can file a separate application for the same subject matter in the US, Japan, Australia and Thailand (and indeed in almost every other country) by January 16, 2000 and link it to the original Philippines application. This means that the effective first date for the foreign applications can be backdated to the original date of January 17, 1999.

In US patent 6,139,898 (reproduced in the exercises at the end of this Module), you will see that the patent is based on an earlier European patent application, number 98200964, filed on May 27, 1998. So even though the US application was filed on March 26, 1999 (also listed on the patent document), the effective priority of this patent would be May 27, 1998. This means that if a directly conflicting patent application was filed in the US, for example application XYZ filed in January 1999, then XYZ would not normally overturn patent 6,139,898 even though it was filed *in the US* later than XYZ, because patent 6,139,898 could 'claim priority' from the earlier European application.

In the course of processing patent applications, it is not unusual for the material in one application to be transferred to a separate new application – this can be called a 'division' or a 'continuation in part.' In this process, the material that is transferred in this way can bring with it its original priority date. As a result, it is important for the patent document to record details of any earlier application which may affect the patent's effective priority date. On the Cohen and Bayer patent shown above, you can see that it relies on several earlier patent applications and 'continuations in part'. So even though this is based on an application filed in 1979, it could actually claim some priority from applications lodged back as far as 1974, some five years earlier.

Publication date and date of grant

Most countries (and the PCT system) publish applications for patents shortly after 18 months from the earliest claimed priority date. Accordingly, if you apply for a patent in Australia, basing your application's priority date on an earlier patent filed in Thailand in January 2000, then the application will normally be published in Australia some 18 months after the priority date – i.e. in July 2001. Patent information lists the patent publication date which can be very important, as it marks when the information in a patent document entered the public domain.

Until recently, in the US system, patents were not published until they were granted. Accordingly, this patent was published when a decision had been taken to approve the application, and it was published on May 6, 1997. In other words, the first publication date and the date of issuing an approved patent amounted to the same thing. Often, the publication date is long after the application date or priority date – for example, the Cohen and Boyer patent shown above was published in December 1980, on the basis of an application filed in January 1979, but is based originally on an application filed in 1974.

The publication policy has very recently changed in the US. The US Patent and Trademark Office now publishes most US patent applications 18 months after the first priority date.

Classification of the patent

Details of the classification of the invention are set out under the filing date. US patent documents show two classifications. One is for the US patent classification system and the other classification reference is for the international system called the International Patent Classification (IPC). The purpose of classification systems generally and the IPC in particular are discussed in *Module Four: Searching Patent Databases.*

For example, the emu oil patent document shows that the US classification is "424/522:424/DIG.10" and the international classification is "A61K035/12". The IPC classification is in a hierarchy, which leads to the subject matter of the emu oil patent as follows:

Section A: human necessities
Subsection: health, amusement
Class A61: medical or veterinary science; hygiene
Subclass A61K: preparations for medical, dental, or toilet purposes
Main group 35/00: medicinal preparations containing material or reaction products thereof with undetermined constitution
Subgroup 35/12: materials from mammals or birds

Anyone searching for similar technologies – for instance, medicinal preparations extracted from other birds, would be able to locate this IPC classification and search through patents with that subject matter.

The field of search is under the classification references and sets out the codes for the US classification system that the patent examiner searched. For example, in the emu oil patent document the field of search codes are "424/522, 520, DIG.10". This is a record of the fields of technology that the examiner considered relevant to the novelty and inventiveness of the claimed invention.

References "made of record"

References "made of record" in the application process for the patent follow the field of search details. References "made of record" are references that the patent examiner considered in determining patentability of the invention. In the emu oil patent, references of record are certain US patent documents (5 208 209 and 5 346 922) and other references (including the work of Wantanabe et al), which are not patent documents but may be journal or textbook publications.

Claims

At the end of the cover page the number of claims are listed. In the emu oil example there is only one claim – this is unusually brief. The Cohen-Boyer patent shown above has 14 claims.

The Specification

The specification sets out the background to the invention and a summary of the invention. The specification also sets out a detailed description of the invention, which provides a general explanation and provides specific examples of the invention. The specification also includes sequence listings if the invention refers to certain molecules or proteins. Drawings may also be included.

The background

The background describes the present "state of the art" in the field of the invention. It outlines existing technological products or processes in the field of the invention and explains why they are not ideal or how they could benefit from improvement, describing the problem that the new invention addresses. The background helps to highlight the differences between existing technology and the claimed invention, thus supporting the claim that the claimed invention has an inventive quality, and is not an obvious extension of the prior art.

Example – background in emu oil patent document US 5 626 882

TECHNICAL FIELD

This invention is in the field of topical insect repellents. More particularly, an effective, natural and safe mosquito repellent comprising Emu oil is provided.

BACKGROUND ART

This invention relates to a method of repelling insects, and more particularly to a method for repelling mosquitoes using a natural ingredient, emu oil. Known natural oils that repel insects include rotundial (from the leaves of Vitex rotundifolia, Watanabe K et al. (1995) Biotech Biochem 59(10):1979-1980); citronella oil (e.g. U.S. Pat. No. 5,346,922); eucalyptus oil (Watanabe et al. (1993) J. Agric. Food Chem. 41:2164-2166); and oil (Sharma VP et al. (1993) J. American Mosquito Control Association 9(3):359-360); and oil of Hedeoma pulgioides, oil of anisum and oil of chrysanthemum (U.S. Pat. No. 5,208,209).

However, the only active ingredient currently registered by the EPA as a topically applied insect repellent is N,N-diethyl-m-toluamide (DEET). When applied to children's skin, DEET has been implicated in causing convulsions. DEET is also known to react with certain plastics and synthetic rubber and cause skin irritation (Watanabe et al. (1993), supra). As a result of these problems and other side effects, New York State has banned products comprised of 100% DEET.

Accordingly, there remains a need for a natural, safe substance which acts to repel biting insects when topically applied to the skin.

Summary of the invention

The summary of the invention discusses the claimed invention, rather than the disclosure. That is, it is about the unique characteristics that define the invention, and it mirrors the material covered in the claims, particularly the main claims. The summary explains how the new invention solves the problems set out in the Background. It may also note particular advantages of the present invention over the existing technologies, and particularly unexpected properties of the invention.

Example - summary in emu oil patent document US 5 626 882

The summary section of US 5 626 882 is very short and effectively re-states the claims.

SUMMARY OF THE INVENTION

The present invention provides a method for repelling biting insects comprising the step of topically applying emu oil to the skin of a subject.

Detailed description of the invention

The detailed description of the invention explains how to practise it, meeting the basic requirement that a patent applicant must 'disclose the invention in a manner sufficiently clear and complete for the invention to be carried out by a person skilled in the art' (TRIPS) and the obligation in some countries' patent laws to 'indicate the best mode for carrying out the invention known to the inventor' (TRIPS). The applicant has a strong incentive to provide this full description - the patent claims can be held invalid if the disclosure is not sufficient, or if there is inadequate evidence of the utility (industrial applicability) of the claimed invention. The detailed description often provides the basis for more detailed characterisation of the invention in narrower, dependent claims, just in case in the broadest claimed concept is not allowed.

The detailed description provides examples showing how to practise the invention. Examples are not mandatory, and do not limit the scope of the patent, but they do assist in meeting the "enablement" requirements – that is, they help enable the reader of the patent to put the invention into effect. The detailed description is often followed by a statement that the invention is intended to go beyond the embodiment described in the disclosure. For example, in our emu oil example, the patent document says that:

> it will be appreciated by those skilled in the art that the [invention] can be performed within a wide range of equivalent parameter, concentrations and conditions without departing from the spirit and scope of the invention and without undue experimentation. While this invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications. This application is intended to cover any variations, uses, or adaptations of the inventions following, in general, the principles of the invention

> and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains…

It also says in the course of the detailed description of specific examples: 'the following examples are presented as a further guide to the practitioner of ordinary skill in the art, and are not to be construed as limiting the invention in any way.'

This kind of statement is to guard against someone making a minor variation of the patented subject matter which differs in a trivial way from the embodiment of the invention described in the patent document, but still takes the essence of the inventive concept. Without such a statement, they could argue that their variation goes beyond the invention as disclosed in the patent document, and therefore that any claim that extends to their variation is not supported by the patent documentation – and is therefore invalid and so cannot be enforced (see the case study on Hepatitis B antigen in *Module Two*.)

Example - detailed description in emu oil patent document US 5 626 882

The detailed description of the emu oil patent document US 5 626 882 sets out several examples of how aspects of the invention were carried out. One of the examples relates to an experiment performed to determine the effect of emu oil on the frequency of mosquito lands and bites.

BEST MODE FOR CARRYING OUT THE INVENTION

Throughout this application, various publications, patents and published patent applications are referred to by an identifying citation.

The disclosures of these publications, patents and published patent applications are hereby incorporated by reference into this application to more fully describe the state of the art to which this invention pertains.

The present invention provides a method of repelling biting insects using emu oil, a natural and safe substance. In the preferred embodiment, pure emu oil is applied to the skin.

The following examples are presented as a further guide to the practitioner of ordinary skill in the art, and are not to be construed as limiting the invention in any way.

Example 1: The effect of emu oil on frequency of mosquito lands and bites

To determine if emu oil was an effective mosquito repellent, pure emu oil (Zoogen, Inc., Davis, Calif.) was applied to one hand of a volunteer. The other hand was left untreated. Each hand was placed in a nylon mesh cage containing mosquitoes (Aedes aegypti) and the number of mosquitoes which landed and/or bit in 30 seconds was recorded. The experiment was performed in duplicate. Results of the experiments were averaged and are summarized in Table 1.

Table 1

	Emu-oil treated hand (lands/bites)	untreated hand (lands/bites)
Test 1	0/0	11/11
Test 2	1/0	26/26

These results demonstrate that topically applied emu oil is an effective mosquito repellent. It greatly reduces the number of mosquitoes which land, and completely eliminates biting.

Example 2: The effectiveness of emu oil as a mosquito repellent over time

To determine how long topically applied emu oil maintains efficacy as a mosquito repellent, the treated hand was exposed to a cage of mosquitoes at 15, 30 and 60 minutes after application. The number of lands and bites were compared at each time point with the untreated hand. Results from duplicate experiments were averaged and are presented in Table 2.

Table 2

	Number of lands on	
Time after application	treated hand	untreated hand
5	4	18
30	2	12
60	10	12

These results show that emu oil remains an effective mosquito repellent for at least 30 minutes.

Example 3: The effectiveness of diluted emu oil

To determine the effectiveness of diluted emu oil, the emu oil was diluted with ethyl acetate to a fixed percentage, applied to one hand and inserted into a mosquito cage. The number of lands were recorded. The experiments were performed in duplicate at each dilution level. Results are shown in Table 3.

Table 3

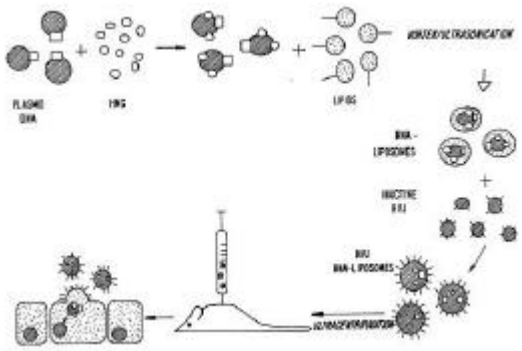
	Number of lands		
Percent emu oil	Exp't 1	Exp't 2	average
0	10	9	9.5
0.50	10	10	10
1.0	5	5	5
5.0	6	4	5
10.0	4	5	4.5
25.0	2	1	1.5
50.0	1	1	1
75.0	1	1	1
100.0	0	0	0

These results demonstrate that dilute amounts of emu oil effectively repel mosquitoes. At a dilution as low as 1%, emu oil reduces by one-half the number of mosquitoes which land. At 25% emu oil, the number of mosquito lands drops to one-tenth of lands on an untreated hand. Thus, emu oil is an effective insect repellent at a concentration of 1% or higher.

Having now fully described this invention, it will be appreciated by those skilled in the art that the same can be performed within a wide range of equivalent parameter, concentrations and conditions without departing from the spirit and scope of the invention and without undue experimentation. While this invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications. This application is intended to cover any variations, uses, or adaptations of the inventions following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth as follows the scope of the appended claim.

Drawings / figures

Drawings or figures are not mandatory in a patent specification. However, they help to explain some information, tool or result set out in the disclosure. Drawings are provided to assist the reader to understand the invention as described. In some countries drawings might be used to interpret the claimed scope of the invention. In the case of the patent we are looking at, there are no drawings, as it was not considered necessary to describe the invention by graphic means.



A drawing from a patent concerning cancer vaccine

Gene sequence listing

For biotechnology patents, effective disclosure of the invention can involve providing the full listing of new DNA, RNA or protein sequences that are relevant to the invention. Disclosure of the full sequence is required when this is necessary to carry out the claimed invention – it is not necessary for every biotechnology patent. In the US patent system, there are distinct disclosure requirements for gene sequence listing includes every disclosed nucleotide sequence more than 10 bases long, and every disclosed peptide sequence more than 4 amino acids long. Sequence listing assists examiners in searching sequences to test for novelty. A sequence listing in a specification is cited in the form “SEQ ID No:1” which is a cross reference for the full sequence listing.

The Claims

The claims are the most important part of a patent document from a legal perspective. The claims mark out the subject matter regarded as the invention over which the patent owner has legal rights. The claims in a patent specification must be precise and clear. This is particularly important so that people know exactly what use of the invention would be infringement and what use would be allowed. It also enables researchers to pursue alternative research paths around the claims. To challenge a patent right that you think is invalid, in most cases you would have to challenge the validity of the claims.

A patent specification must have at least one claim (a provisional patent application can be lodged in some countries – this kind of specification need not have claims, but it must be followed by a complete specification, with claims, if it is to mature into a patent right). Each claim must be only one sentence, although it can be very long and complex, if this is necessary to define the essential features of the invention. Claims can be very difficult to read because of this complexity, and also because they use abstract language rather than concrete language. If a claim referred to a 'screw' rather than 'fastening means,' then someone might easily get around the patent by doing exactly what the invention entails, but using a bolt or rivet instead of a screw. As a result, patent claims tend to use abstract terms like 'fastening means,' to ensure that their legal scope is sufficiently broad.

Claims can be independent or dependent. Independent claims are complete in themselves, and do not need to be read with reference to any other claim. For example, in the European Harvard Onco-mouse case (see *Module Two*), claim 17 concerned 'a transgenic non-human mammalian animal whose germ cells and somatic cells contain an activated oncogene sequence introduced into the said animal, or an ancestor of said animal, at a stage no later than the 8-cell stage.'

Dependent claims further limit a preceding claim, to make it more specific. In the same case, claim 18 is directed to 'an animal as claimed in Claim 17 which is a rodent.' If, in this case, a court found that claim 18 was too broad, based on the specification, then it might still allow Claim 17 to be valid, as it is more specifically based on the disclosure (and on the preferred embodiment disclosed in the specification). Conceivably, such an invention could not work on other mammals, due to technical barriers unforeseen by the inventors - this could mean that the claim could be held invalid due to lack of utility. However, since the research work had already been done on rodents, they could be confident that a claim directed at rodents could not be held lacking in utility.

Patent claims may either be for a process (or method), or a product. It is quite common for a patent to claim both a process and a product, united by the same underlying inventive concept. For example, the rice patent in the exercises of Module Two claims both a method of breeding a rice plant, and the result of that process – the rice plant itself. The legal effect of these claims differs considerably – a claim to a product potentially controls any dealing in the claimed product, and a process claim covers use of the process itself. The patent right also generally extends to use and commercial dealing with a product directly produced by a patented process.

Example - claims in emu oil patent document US 5 626 882

There is only one claim in the emu oil patent; it is one brief sentence, claiming a process:

A method for repelling biting insects comprising the step of topically applying emu oil to the skin of a subject

In this case, there is no dependent claim. A dependent claim would define the invention more closely, just in case the broader 'main claim' is held to be too broad and is found to be not novel, lacking utility or not supported by the disclosure of the invention. In this case, a dependent claim could read: 'The method as claimed in claim 1, wherein the method is used to repel mosquitos.'

The patent does not have a product claim for emu oil as such as an insect repellent. It would be impossible to sustain a product claim on emu oil as such. Emu oil is a known substance and is plainly not novel. However, in some legal systems, someone selling or supplying emu oil fully knowing that it is going to be used to infringe a patented method or process could be held liable for 'contributory infringement' – knowingly contributing to an infringing act. The situation would also be different if the patent had disclosed a new and inventive process for treating emu oil to make it particularly effective as an insecticide, for instance – then it might be possible to get a patent for that process, and for the modified emu oil created by that process.

3.3 How is the scope of the patent claim determined?

Patents serve to disclose technical information, and to define the scope of a legal right. How you read a patent specification is very different, depending on whether you are searching for information, or whether you are concerned about the nature of the patent right. If you are just looking for technological information, it is probably best to focus on the abstract, the background and the description. If you need to interpret the scope of a patent, then the first place to look is in the claim or claims. But from a legal point of view, the patent document does need to be considered as a whole, and the descriptive material in the patent can influence how the claims are interpreted.

There are significant differences between countries and jurisdictions on how patent claims are interpreted, and it is vital to consult a qualified legal advisor, with specialist patent experience, before making a judgement about the scope of validity of any patent rights.

How is the scope of the claims determined?

The claims point out and distinctly claim the subject matter regarded by the applicant as the invention. The claims define the borders of the claimed territory. Initially, 'claims' are just that – as part of an application or request for a patent right, the applicant asserts or claims that they are entitled to patent rights of that scope. That doesn't mean they will get what they have asked for. Particularly when you are looking at a patent application, rather than a granted patent, it is important to remember that the scope of the claims as applied for can often be reduced, and in some cases found to be invalid. The claims can be tested at three stages:

- During examination by the Patent Office;
- During a period for opposition to the patent by third parties (either just before or after the Patent Office approves the application), or similar procedure such as re-examination in the US Patent and Trade MarkTrademark Office; or
- In court proceedings, either when the patent holder takes out an infringement action, or when a third party takes direct action to have the patent overturned.

At each stage, there is a possibility that the patent claims will be held to be completely invalid and the patent right denied or cancelled, or that the scope of the patent claims will be reduced to take account. This could be due to further publications being brought forward to show that the patent

as claimed was not novel or not inventive, or due to a finding that the patent claims were too broad in scope to be supported by the technological information provided in the patent document.

Some national administrations elect not to examine patent applications for their validity, and effectively leave the matter up to the applicant to determine what to claim – applicants have an incentive to be responsible in the scope of their patent claims, because if you try to enforce a clearly speculative invalid patent, the legal action would rebound on you, with the court almost certain to cancel your patent rather than enforce it. In these systems, the patent applications are generally checked only to ensure that the application appears to provide correct administrative information and that certain requirements, such as the payment of fees, have been undertaken – this is known as 'formality examination.'

In many countries, the Patent Office does examine patent applications to reach a conclusion on whether the substance of the claimed invention appears to be eligible for a patent – this is known as a 'substantive examination.' In these systems, the patent examiner (who will be familiar with the general field of technology) must be satisfied that the patent meets the legal requirements for a patent. As discussed in *Module Two*, an invention must be novel, involve an inventive step, and be capable of industrial application to be eligible for patent protection. The patent specification must also disclose details of the invention in such a way that a person skilled in the art (that is, the field of technology of the invention) can reproduce the invention.

A patent examiner assesses whether an invention is novel and involves an inventive step by considering the "prior art" in the field. "Prior art" in patent law refers to the published documents and common general knowledge in the field of technology related to the invention before the priority date of the patent application. In most jurisdictions, the examiner can refer to prior art documents that are published anywhere in the world, and patent offices generally have access to extensive collections both of patent documents and other scientific and technological publications.

It is not unusual for the applicant to make claims broader than the patent examiner is able to allow. This leads to negotiation between the applicant and the examiner during the examination stage, often resulting in narrower or more clearly defined claims, which the applicant submits as amendments to the patent document. For instance, these amendments might be introduced to deal with an examiner's objections that:

- the claims as drafted are not sufficiently different from the existing prior art and therefore cover material which is either novel or lacking an inventive step; or
- the claims as drafted are not fully supported by the material disclosed in the specification, or lack utility.

In some cases, it proves impossible for the applicant to find amended claims that are acceptable to the examiner, and in these cases the application is refused and does not produce a patent at all. (Such decisions can be challenged by appealing to a court – this happened in the case of the Chakrabarty case described in *Module Two*.)

Patent examiners consider other issues – for instance, the patent specification might actually contain more than one invention. This leads to an objection for lack of unity of invention. In these cases, the patent specification can be amended to focus on one of the inventions disclosed in the patent, and the other material can be covered in a separate application, one that is 'divided out' of the original application, and still keeps the same priority date (assuming that the second invention is derived from the technical information disclosed in the original application document). This separate application can be called a 'divisional' application.

Once the patent is granted, the claims tell you what rights have been considered by the Patent Office as suitable scope for an exclusive right.

In summary, the scope of the patent right is contained in the claims that are allowed by the patent office once it has searched the prior art and examined the patent application. In most countries, the patent examiner considers the application for patent protection for a claimed invention in light of:

- the prior art, and
- the description set forth in the specification,

to determine whether the claimed invention is novel and involves an inventive step, and is properly based on or supported by the disclosure. If a claim is too broad, and therefore incorporates matter outside the claimed invention, then it may be determined that that particular claim is not valid, and an amendment to the patent document will be required. For example, if one of the claims in the emu oil example was for the use of emu oil as a topical antiseptic or as a skin balm, then this would not be considered to be within the scope of the disclosed invention, which is for a method of using emu oil as an insect repellent.

The scope of the same patent can be different in different countries

An important point to remember in assessing the scope of a patent is that the scope of the same patent for the same invention can be different in different countries. This is largely due to the territorial nature of the patent right, and the different law and interpretation of legal principles in different countries. There may also be different pieces of prior publications or other disclosures that could be raised in different countries. Due to these differences throughout the world the intellectual property strategy of a patent owner will need to be different for different countries.

Interpreting the scope of a patent is needed to determine 'freedom to operate'

The scope of a patent also assists when you are checking whether commercialising your invention is likely to infringe the claims of an existing patent. It is inevitable that patented inventions build to some extent on existing technology, some of which may be patented. Therefore, even though you have a patent for your invention, you might still need the permission of another patent owner of a technology to use their technology in your invention before you commercialise it. Even if you do not have a patent and do not intend to get one, you may still need to check whether there are any patents which could prevent you from pursuing a course of action in developing and commercialising your technology. This issue is known as "freedom to operate" and is discussed in detail in *Module Eight Researching and Intellectual Property*.

If your commercial activity is likely to infringe the claims of an existing patent owner you need to consider your options. One option is to seek a licence from the patent owner to use their technology and pay the patent owner for it. Another option is to "invent around" the existing patented technology by finding an alternative path to the same goal so that you do not need a licence and your commercial activity will not infringe an existing patent. In exceptional situations, freedom to operate is secured by court action to revoke the patent right or to secure a compulsory licence under the patent.

3.4 How are patent documents used?

As can be seen from the discussion above, the different sections of a patent document serve different purposes and address the needs of different people. The detailed description shows what the applicant believes is their invention and tells other researchers how to practise it. The claims tell you what the Government (through the Patent Office) is prepared to grant as the proprietary territory, that is, the claims in a granted patent set out the scope of the actual legal patent rights.

Researchers: scientific perspective

For researchers, patent literature is a great source of scientific data. The detailed description in a patent specification can provide researchers with ideas for their own research. As outlined in *Module Four: Searching Patent Databases*, there are many databases that provide information about patent documents. For example, the USPTO patent database is a major source of information about patent documents.

Researchers need to remember that the term of a patent is only 20 years from the first filing date. After that time a patent is in the public domain, which means that researchers can use the descriptions in such patent specifications to commercialise inventions based on expired patent applications.

The Patent Office: administrative perspective

The cover page is very important from the administrative perspective of a patent office. Access to clear and accessible patent information is very important for the granting and maintenance of patent rights. For example, the classification codes on the cover page of a patent document are essential to the patent process. An invention must be classified correctly to enable an effective prior art search by a patent examiner who might need to access that patent document when examining a later patent application in the same field of technology.

Lawyers: legal perspective

As noted above, the claims in a patent document set out the legal boundaries of the patent right. From a legal point of view the claims are the most important part of a patent document. If ever you need to enforce a patent over your invention against an infringer, or if your own activities are challenged by a patent holder as being an infringement of their patent, the first questions to consider are: is the patent in force; and, what is the scope of the claims?

3.5 What is the process for getting a patent?

If you only wish to protect your invention in one country, then the matter is relatively straightforward – you file an application in the national Patent Office, and undertake the necessary steps at the national level to get a national patent. This process is described in relation to Australia below. The exact procedure differs between countries, and the Australian procedure is described just to illustrate one approach, which is similar to the procedure in many other countries. Apart from formalities – ensuring that the applicant has paid the right fees and the documentation is in order – these procedures normally include the kind of examination process outlined in the section above.

If you want to protect your invention in a number of countries, then patent protection becomes more complex and can become very expensive. There are two important legal mechanisms that help reduce this complexity and to some extent reduce or delay the major costs. One is the Paris Convention right of priority (which all WTO Members and all Paris Convention signatories have available), and the other is the Patent Cooperation Treaties (which is available to nationals and residents of the 111 PCT signatory states)

Getting patent rights internationally

Patent rights only have legal effect in the country (or region) in which they are applied for. If you need to protect your patent in Japan, Republic of Korea, Malaysia, Singapore, Thailand, and the Philippines, you would eventually need to file a separate application for the same invention in each of these countries. The grant of a patent in any one of these countries has no legal effect in any other of these countries. To get literally 'worldwide' patent rights, you might need to apply for patents in over one hundred countries or regions.

Europe, Eurasia, and Africa have regional arrangements that mean that a patent can be granted with regional effect. For example, 19 European countries are members of the European Patent

Convention (EPC) - Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Liechtenstein, Luxembourg, Monaco, Netherlands, Portugal, Spain, Sweden, Switzerland and the UK. Under this system, you can make a single application with the European Patent Office (EPO), based in Munich, which leads to a bundle of national patent rights.

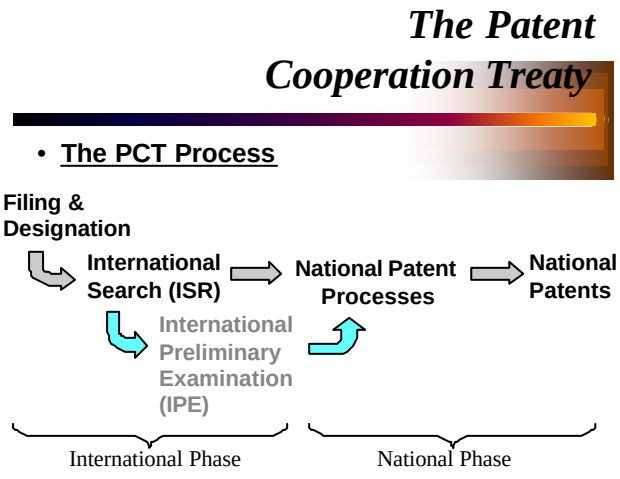
To make it easier to file patent applications internationally, it is possible to 'claim priority' from earlier patent applications in other countries, but only if you apply within one year. This right to claim priority is created under the Paris Convention (incorporated also into TRIPS), and is often described as 'Convention priority.' So if your first patent application was filed in the Philippines in March 1999, you would have only twelve months to file applications in every other country you are interested in. This is preferable to filing applications in every country at the same time (which would be highly impractical and expensive), and it does give a certain amount of time for the inventor to assess the viability of the invention and to secure financial support. However, it is still a major decision to make early on in the life of an invention. If, in our example, you decided not to file an application in China within that twelve-month period, and only became interested in the Chinese market two years later, it would be impossible to gain effective patent rights in China. So the decisions made early in the life of the patent are extremely important, and a decision not to pursue patent rights in a country can rarely be reversed. This is a problem, because it is difficult to take such decisions with confidence, and to raise the necessary funds, so early in the life of a new invention

PCT Applications

The PCT addresses some of these problems and provides an alternative system that simplifies the initial steps in gaining international patent protection. This system is only available to nationals or residents of those countries which have acceded to the Patent Cooperation Treaty (these are listed in a box below); they can make international applications which designate any or all of the PCT countries. PCT international applications can also designate regional patent systems, such as the European Patent Office.

If you want to apply for patent protection under the PCT, the patent process is usually divided into two stages:

- the international phase, and
- the national phase.



In the PCT's international phase you can lodge a single international patent application, which preserves your right in all the countries you designate on your application. To keep your options fully open, you can designate all 111 PCT countries, at a fraction the cost of filing a separate application in each one. In effect, this reserves the earliest priority date in each of those countries to safeguard your rights when you later seek protection at the national level. Applicants often keep their options open when filing a PCT application by designating all PCT countries, even though they are highly unlikely to pursue patent rights in all of them. But the PCT system gives some breathing space for them to assess the commercial merits of the invention and to sound out potential markets, before committing finances to separate national applications.

After the international phase is completed, you must enter the national phase in those countries where you have decided to pursue patent rights. In the national phase you have to comply with

the separate requirements for patent protection in each country in which you want patent protection, although the process is streamlined in comparison with starting a stand-alone new application in that country. As your rights in national patent law are linked to the priority date of the original international application, other peoples' activities in the meantime cannot impair your patent rights. As you will remember from *Module One: Introduction to Intellectual Property*, the PCT application process provides a number of benefits to patent applicants but it is only a streamlined **application** process. There is no such thing as a "world patent", which is why you have to go through the substantive parts of the patent process in each country where you and your commercial partners and supporters desire protection.

The 111 Parties to the PCT as at 17 April 2001 were (*APEC Economies highlighted*): Albania, Algeria, Antigua and Barbuda, Armenia, **Australia**, Austria, Azerbaijan, Barbados, Belarus, Belgium, Belize, Benin, Bosnia and Herzegovina, Brazil, Bulgaria, Burkina Faso, Cameroon, **Canada,** Central African Republic, Chad, **China,** Colombia, Congo, Costa Rica, Côte d'Ivoire, Croatia, Cuba, Cyprus, Czech Republic, Democratic People's Republic of Korea, Denmark, Dominica, Ecuador, Equatorial Guinea, Estonia, Finland, France, Gabon, Gambia, Georgia, Germany, Ghana, Greece, Grenada, Guinea, Guinea-Bissau, Hungary, Iceland, India, **Indonesia,** Ireland , Israel, Italy, **Japan,** Kazakhstan, Kenya, Kyrgyzstan, Latvia, Lesotho, Liberia, Liechtenstein, Lithuania, Luxembourg, Madagascar, Malawi, Mali, Mauritania, **Mexico,** Monaco, Mongolia, Morocco, Mozambique, Netherlands, **New Zealand,** Niger, Norway, Poland, Portugal, **Republic of Korea,** Republic of Moldova, Romania, **Russian Federation,** Saint Lucia, Senegal, Sierra Leone, **Singapore,** Slovakia, Slovenia, South Africa, Spain, Sri Lanka, Sudan, Swaziland, Sweden, Switzerland, Tajikistan, The former Yugoslav Republic of Macedonia, Togo, Trinidad and Tobago, Turkey, Turkmenistan, Uganda, Ukraine, United Arab Emirates, United Kingdom, United Republic of Tanzania, **United States of America,** Uzbekistan, **Viet Nam,** Yugoslavia, Zimbabwe.

The PCT also provides for designation of the EPO, the Eurasian patent system, and two African regional patent systems (OAPI and ARIPO).

The International Phase

As we have noted, the PCT makes it possible to apply for patent protection in many countries at the same time by filing only one international patent application rather than having to file separate applications in each country that protection is sought. This streamlined application process provides many advantages to patent applicants. If applicants prepare their PCT application process in line with the PCT standards it is possible to comply with a number of formalities in a centralized manner. This means that the costs of applications are reduced.

As noted above, another benefit of the PCT application process is that it provides for an internationally recognised priority date which has effect in each country you have designated. The priority date was discussed in *Module Two*. It is an important concept in the patent process because it establishes the earliest date from which your right can be recognised if you are granted a patent.

There are three main stages in the international phase. They are:

- filing a PCT application and designation of countries in which protection is sought
- the international search, and
- an optional preliminary examination.

The diagram below shows the three main stages of the PCT process and shows that they can be followed by the national phase, which involves patent applicants complying with the requirements of national patent systems.

Filing and designation

The first stage in the international phase is for a patent applicant to file a PCT application with the authorised "receiving office" – this can be a national patent office or the secretariat of the World Intellectual Property Organisation (WIPO) in Geneva. At this stage the applicant also designates the countries in which they would like a national patent. The only countries that can be designated are countries that are members of the PCT. This is not a binding commitment to proceed in each of these countries – but it keeps open the legal option of later gaining patent rights in each designated country.

If a PCT application is not used, applications for patent protection need to be made for each country, including translating the document into the language of each of the countries in which patent protection is sought. Translation costs can be very expensive, particularly because of the technical nature of language that describes technology. A major advantage of a PCT application is that the application is in one language only, which saves the patent applicant time and money at the beginning of the patent process. It does not necessarily save the ultimate costs of translation and other formalities, but it delays them to a point when the patent is more likely to be generating income and there is more confidence as to its validity.

International search

After filing and designation, an international search is conducted on the international application by one of the International Searching Authorities (which are certain designated national patent offices), and an International Search Report is issued. A key part of the streamlined PCT process is that these search results are provided within nine months of filing. The timing of these search results is very valuable to the applicant because it gives the applicant a good idea, early on in the patent process, about whether they should proceed with the patent process, or whether they can make amendments to their claims to enable them to patent their invention. The early timing of the international search results allows the applicant to make such changes early in the patent process, before the major expenses of the national phase of the patent process begin. Once the search report is available, the applicant can make an amendment to the claims (not to the rest of the specification) and submit a brief statement concerning the amendments. When the international search report throws up unexpected prior art that potentially causes problems for the original application as filed, this saves the applicant a great deal of trouble and expense – either they can decide it's not worth proceeding with the application (and they save the immense cost of filing applications in many countries), or they are able to focus the claims in a way that will improve their chances of being accepted nationally (and they save the cost of amending many separate applications in each national patent office.)

Example - international search on a mouse-trap patent application

Imagine that an independent Vietnamese researcher, called My Vanh, invented a mouse-trap that automatically covered the mouse when it gets trapped. The purpose of the automatically closing cover was to make a more hygienic mouse-trap than traditional mouse-traps that leave the dead mouse in the trap out in the open. My Vanh had been working on this invention ever since her 2 year old son was found playing with a dead mouse in a mouse-trap a few years ago.

My Vanh thought that there would a big market for her invention in several countries. She was worried about other researchers copying her good idea and so she decided to apply for a patent to protect the intellectual property rights in her invention. She filed a PCT application and designated Vietnam, China, Japan, Indonesia and Australia as the countries in which she wanted to seek a national patent. However Malaysia is not a member of the PCT system, so My Vanh has to make a separate application for Malaysia within twelve months from the first application, using her priority rights under the Paris Convention (to which Malaysia is bound).

Within nine months of filing her PCT application, My Vanh got the results of international search report on her mouse-trap. All the prior art that the search listed seemed to be different from her invention, in that no-one had solved the problem in a comparable way.

On the basis of the results of the international search, and after speaking to a patent attorney, her commercial adviser and a financial company, she decided to pursue getting a patent in Vietnam, Indonesia and China by 'entering the national phase' in these countries, but not to pursue the application (or enter the national phase) in Australia and Japan because she concluded that her competitors were unlikely to manufacture the mouse trap in those countries due to relatively high manufacturing costs, and her limited funds meant that she could not afford the cost of patenting there.

Optional international preliminary examination

The third key feature of the international phase is that an applicant can choose to get an international preliminary examination of their invention. This is an optional step.

The purpose of the international preliminary examination is to consider the international search results and provide an opinion on whether the invention is likely to be patented. The international preliminary examination assesses in detail the invention against the prior art found in the international search and concludes whether the invention appears to satisfy the legal requirements for a patent, namely, novelty, inventive step and industrial applicability. As discussed in *Module Two*, it is not a binding legal determination, but merely an indicative tool for the applicant.

The National Phase

If a patent applicant decides to pursue patent protection after the international phase, they must comply with the patent laws in each of the countries in which patent protection is sought.

It is not compulsory to proceed with the national phase of the patent process after the international phase is completed. Nor is the international phase a compulsory part of the patent process. For example, a patent applicant might choose not to use the PCT process and apply individually to the national patent office in each country in which protection is sought.

After the PCT international phase, an applicant may decide not to seek patent protection. They might decide this if the results of the international search showed that their invention was already patented, meaning that their invention would not be able to get a patent. Alternatively, after the international phase, a patent applicant might decide to still try to get a patent in each of the countries that they designated on their PCT application form.

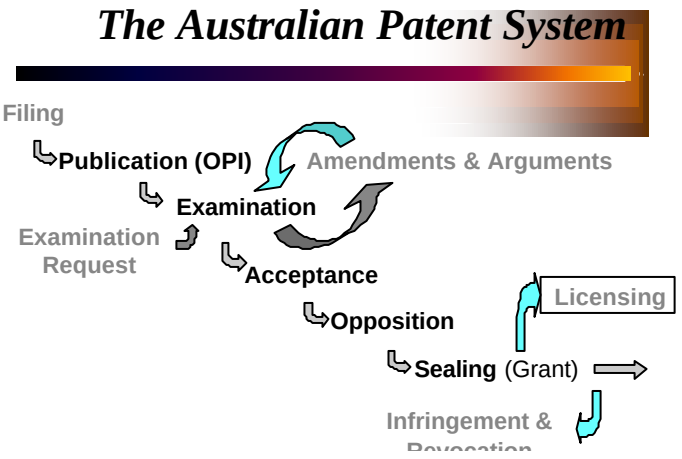
As discussed in *Module Two: Biotechnology and Intellectual Property* and noted above, the TRIPS Agreement provides only broad obligations in relation to the protection of patents. That is, TRIPS provides that patent protection be given to inventions that are new, involve an inventive step and are capable of industrial application. These general tests can be implemented and interpreted in different ways in different countries, and can be influenced by different legal traditions. This flexibility means that the detail of patent law is different in different countries. The process for getting a patent also differs in different countries. However, as there are similarities in the general stages in a patent process it is useful to study the process in one country to understand the steps in the national patent process.

A case study of the patent process in the Australian patent system is discussed below for this purpose. The diagram below summarises the steps in the Australian patent process system.

Application

The first step you need to take in the Australia patent process is to file an application for patent protection with IP Australia. The patent office in Australia is in IP Australia, which is a Government body. You need to get advice from a patent attorney before applying for a patent. A patent specification is a very technical document that is usually drafted by a patent attorney.

Officers in IP Australia will check your patent specification to see if there are any problems. For example, if some of the pages cannot be read properly IP Australia will ask you to fix the problems.



Examination

In Australia it is up to you, as the applicant, to request examination of your patent application. Applicants usually request examination of their specification 1-2 years after the complete specification is filed. During examination, a patent examiner in IP

Australia checks the application to see that it meets the Australia patent requirements. The patent examiner checks that:

- the invention is novel;
- the invention involves an inventive step;
- the invention involves a manner of manufacture (this is the equivalent of the TRIPS requirements that an invention must be capable of industrial application);
- the description is sufficiently clear and complete;
- the claims are for one invention,; and
- the claims are supported by the description of the invention.

Please see *Module Two: Biotechnology and Intellectual Property* for details on how to meet the substantive legal requirements of novelty, inventive step and industrial application. IP Australia usually provides a response to a request for examination in 5 months from the date of the request. The reply will either be acceptance of the application or an adverse report. An adverse report sets out reasons why an application is not accepted. For example, examination might result in an adverse report if the patent examiner finds out that the invention is not novel, on the basis of a publication that was found in the search for prior art.

You, as a patent applicant, might not agree with parts of the examiner's adverse report. If this happens, you can put your views to IP Australia and try to get them to amend their findings. Alternatively, you might need to amend your patent application to address the findings in an adverse report. For example, you might need to narrow the claims in your patent application to make sure that your claimed invention is novel. It is very common for patent applicant to make wide claims in their initial patent specification which need to be narrowed during the examination process.

Example – examination of a patent application for a sun block cream

Imagine that a Japanese biotechnology company, called "Beach Biotech", invented a new sun block cream. Beach Biotech applied in Australia for a patent for this cream. It claimed a new sun block cream that prevents sun-burn for a full day, moisturises the skin, and prevents sand from sticking to the skin. The cream uses a key ingredient extracted from seaweed found off the coast of Japan. Beach Biotech worked on this cream for 10 years. They know that there is a very large market for sun block creams in Australia and South-East Asia because of the good weather and beautiful beaches there, coupled with increasing concern about skin cancer. Consumers frequently complained about sand sticking uncomfortably to the skin when they used regular sun creams.

Alana, a patent examiner in IP Australia, examined Beach Biotech's specification. She first did a "prior art" search of publications and patent databases. She found no publications relevant to the claim of the key ingredient as a long-lasting sun-block that prevents sand from sticking. But she did find that a Singaporean cosmetic company called "Skindred" had already patented a skin cream using an ingredient chemically very similar to the Beach Biotech product, claiming its use as a moisturiser. Alana gave Beach Biotech an adverse report on the grounds that the Skindred patent made the Beach Biotech claim either not novel or obvious. Beach Biotech responded by amending its specification to omit any claim to the cream's moisturising effect, and narrowed their claims to distinguish them fully from the disclosure in the Skindred patent.

Publication

Publication of patent documents is a key part of the policy behind the grant of patent rights. Legal rights are granted to patent owners for a limited period of time in exchange for disclosure of details of the invention so that members of the public can benefit from being able to make the invention after the term of patent protection has ended.

Publication of patent documents occurs at different stages of the patent process in different countries. In Australia, for example, IP Australia publishes a patent application about 18 months after its earliest priority date. Patent applications are published in the Australian *Official Journal of Patents* and are available on the IP Australia web site. Publication is sometimes referred to as "OPI", which means "open for public inspection". This version of the patent document bears the document code 'AU-A.'

Acceptance

After examination, if a patent examiner is satisfied that all the legal requirements for patent protection are met, the patent application is "accepted" by the Patent Office. For example, in Australia when a patent examiner accepts a patent application a notice is put in the Australian *Official Journal of Patents*. The patent application is published in the accepted form, with the code 'AU-B.'

Opposition

In patent systems around the world after a patent application is accepted by a patent office there is an opposition period. The opposition period allows members of the community to object to the granting of a patent.

In Australia, after IP Australia accepts a patent application there is a 3-month opposition period. During this time others can start proceedings to show that the invention should not be granted because it would not be a valid patent grant. In Australia a very small number of accepted patent application are opposed. In some other countries, the opposition period comes after the grant of patents – that is, after the patent is actually issued ('post-grant opposition').

Example - opposition to a patent application for a sun block cream

For example, imagine that IP Australia had accepted the patent application from the Beach Biotech patent described above, with the patent claims narrowed to deal with the examiner's initial adverse report. On 1 July 2000 the patent specification was published in the Australian *Official Journal of Patents*. On 1 September 2000, the Singaporean company, Skindred, lodged a notice of opposition to the grant of the patent. Among the reasons given for the opposition was that they had used a similar cream in Australia before the date of the Beach Biotech patent application, and that this made the Beach Biotech invention either non-novel or obvious. Users of the patented Skindred cream had noticed its use as a sun block, and Skindred had promoted this quality in advertisements – it did not apply for a further patent for this quality, because it had already been used in public and would not have been novel. But it was concerned that the Beach Biotech patent would damage its interests.

In the course of opposition proceedings before a hearing officer at IP Australia, Skindred produced evidence that their cream had a similar active ingredient and was used in Australia before the Beach Biotech priority date. They argued that the close chemical similarity of the ingredients meant that it would be obvious to try the ingredient used by Beach Biotech in their product. The opposition was resolved in favour of the opponents, Skindred, and so a patent was not granted to Beach Biotech. Beach Biotech asked its patent attorneys and lawyers in Australia for advice on whether it should appeal to the Australian Federal Court to try to have this decision reversed.

Grant of a patent

In Australia, if there is no opposition to the accepted application IP Australia will seal the patent application and give the patent applicant a patent certificate. The patent rights last for 20 years from the date the application was filed. In very limited circumstances, this term can be extended to compensate for time taken to gain regulatory approval for a patented pharmaceutical.

Payment of fees

The national phase of a patent process does not come cheaply. In all countries, up-front fees must be paid at various stages of the application process and annual fees must also be paid to maintain a patent once it has been granted.

For example, in Australia the main fees for the patent application process are:

- Filing provisional application: $80
- Filing a complete application: $280 (plus a fee of $12 for every page over 30 pages)
- Request for examination: $290.

Fees must also be paid annually to maintain a patent with IP Australia. The IP Australia fees for maintaining a patent range from AUS$165 for the 5th anniversary of the filing of a patent to AUS$790 for the nineteenth anniversary. IP Australia provides a rough guide to estimated total costs. In their view, the estimated total cost of applying for and maintaining a standard patent is about AUS$12 000- $15 000. These estimated costs include about AUS$5 000-$8 000 for applying for a standard patent, which includes attorneys fees, and an additional AUS$7 000 to maintain the patent for its 20 year term. These costs can vary widely, and in particular can be much more than this, depending on what happens in the processing of the application and the need for professional input from patent attorneys.

3.6 What is the role of a patent office?

Apart from their role in examining patent applications and granting patents, patent offices have a range of other responsibilities.

Grant of Patents

The primary role of a patent office is to grant patents. As discussed above, applicants must apply to a patent office for a patent. The Patent Office examines the patent application to see if the invention satisfies the requirements for patent protection. If the Patent Office is satisfied that the invention meets the patent requirements of novelty, inventive step and industrial application, and there is no opposition, the Patent Office grants a patent.

Other Responsibilities

Patent offices also:

- raise public awareness of intellectual property;
- negotiate and maintain international intellectual property treaties, including the Patent Cooperation Treaty (PCT), the Budapest Treaty on the Deposit of Microorganisms and the Paris Convention for the Protection of Industrial Property;
- contribute to the development and implementation of government initiatives aimed at promoting economic wealth through better utilisation of intellectual property;
- consider the advice provided by overseeing and advisory bodies, which may be made up of representatives of the patent attorneys' profession, major customers, representatives of associations of inventors or licence holders, government and experts in the area of patent law;
- maintain a register of valid patents to establish and maintain enforceable rights;
- provide clear, and accessible patent documentation and advice to permit the granting of valid foreign patent rights in the light of the recognition of such "world wide publication",; and
- provide services, especially examination services, to countries where the demand for patents does not justify setting up their own patent offices.

3.7 Summary of Module Three

Structure of a patent document

- **the cover page and abstract**: sets out administrative details regarding the claimed invention, including names of the inventors, assignees, patent number, filing date and classification code
- **the specification**: sets out the background to the invention, a summary of it and a detailed description of the invention
- **the claims**: set out the invention over which the patent owner has legal rights.

Interpretation of the scope of a patent document

- you need to interpret the claims in a granted patent to work out the scope of a patent
- this is necessary because you need to know how the patent document marks out the boundaries of your or someone else's (that is, you need to be able to work out if you have "freedom to operate")
- how you read a patent document depends on what you need to use it for, for example:
    - to a researcher the description is the most important part of a patent document because it provides technical details about how to practise an invention;
    - to a patent office, the cover page, including for example, accurate classification codes, is important to ensure the patent system is reliable and useful, and
    - the claims are most important from a legal perspective because the claims mark out the boundaries of the legal rights in a patented invention.

The steps in the patent process

- there is no such thing as a world patent and so the legal requirements for patenting need to be complied with in each country in which patent protection is sought (there are several regional patent systems which provide a regional patent with effect in the national law of the countries in the region)
- **national applications**: a typical patent application process entails: filing an application for with the national patent office; publication of the specification for public inspection; examination of the application by a patent examiner; acceptance by the examiner if all the legal requirements for patent protection are satisfied; an opposition period (immediately before or after grant of the patent) which allows others to show why a patent should not be granted; and the grant of patent rights and issuance of a patent document.
- **international applications**: applicants who are nationals or residents of Patent Cooperation Treaty (PCT) countries can file a single international PCT application, which designates the PCT countries in which patent protection is sought. An international search for prior art is conducted and an optional non-binding international preliminary examination is also available. The applicant can choose whether or not to convert this application into individual national applications in any or all of the designated countries.

Role of a patent office

- the primary role of a patent office is to grant patents
- other responsibilities include raising public awareness of intellectual property, negotiating and administering international treaties, contributing to Government initiatives, maintaining valid register of patents and cooperation with foreign patent offices.

3.8 Group Exercises - Module Three

Module 3 provides information about reading a patent and the patent process. Please discuss Module 3 with your fellow participants and write out answers to the following questions.

Exercise 3.1 - how to read a patent document - cover page

Thuy-Quyen is researching rice at the Institute of Agrobiological Science in VietNam. Her research team is interested in new developments in the rice market, and in particular at ways of turning rice into a more value added export product - one area of interest is in processing rice so that the consumer can prepare it more quickly than normal cooking. They have a particular interest in the US and European markets. She has searched the USPTO database and has found a patent document called "full moisture shelf stable rice product" (US Patent No: 5 677 338). Her boss has asked her for information about this patent. Please read the patent document (attached to this exercise) and consider the following questions.

(i) What are the various serial numbers on the patent document? What do they mean?

(ii) Who are the inventors?

(iii) Who owns the patent? Is the inventors themselves?

(iv) When was an application filed for the US patent? What is its earliest priority date? What application is this priority based on?

(v) What are the IPC and US classification of the patented subject matter?

(vi) What technological areas did the patent examiner search in when examining the patent application?

(vii) What publications were found to be relevant to this invention – do these include US patent documents, patent documents in other countries, and other non-patent forms of publication? Does this include the background technology described by the applicant in the patent description?

Exercise 3.2 - how to read a patent document - specification

Thuy-Quyen needs to report to her colleagues on the technological information contained in this patent document, during a seminar on new developments in rice processing technology.

(i) What kind of descriptive information is contained in this document, and in what sections?

(ii) Does it describe how to carry out the invention in a way that could be understood by an expert like Thuy-Quyen?

(iii) Do the other documents mentioned (earlier patent documents and journal articles) look like they could be of interest for the seminar?

Exercise 3.3 - how to read a patent document - claims

The Institute is interested in exploring this area of rice processing technology. Thuy-Quyen is asked to analyse the claims of the patent.

(i) Identify the claims – how many independent and dependent claims are there?

(ii) In what ways do the dependent claims narrow or more closely define the material covered in the independent claims?

(iii) Do the claims concern a product or a process? Can you identify a common inventive concept that all the claims share?

Exercise 3.4 - scope of a patent

The Institute is concerned to know the likely legal impact of this patent on any product they develop. Thuy-Quyen is required to draw up a preliminary analysis of the scope of the patent.

(i) How should she analyse the scope of the patent right? What is the technological problem is it proposing a solution for?

(iii) What parts of the patent document should she analyse in determining the scope of the patent right? Why?

Exercise 3.5 - steps in the patent process - the international phase

Nizam, a researcher at the Institute of Biological Science in Singapore, has created a new ointment to heal wounds from burns. The Patent Committee of the Institute has sought advice from a patent attorney, who conducted a search of patent documents and other publications on medications. After the patent attorney advises that she thinks the new ointment will probably satisfy the legal tests to get a patent, a patent application is filed in Singapore. The Institute then explores the commercial received advice from its commercial adviser that there is likely to be a worldwide market. On the basis of this advice and after confidential discussions with a potential financial backer, the Patent Committee decided to seek patent protection in Japan, Malaysia, Indonesia, Thailand, Vietnam, the Philippines, Australia, the US, Germany, France and the United Kingdom. But it needed some time to finalise the commercial deal and investigate approval processes for the new product.

(i) Check the list of PCT member states. Can the Institute pursue patent rights in each of the countries it is interested in? What options are there for countries not in the PCT? Are there any regional arrangements the Institute can use to reduce costs?

(ii) What are the steps in the international phase of the patent process?

(iii) Can the PCT give the Institute of Biological Science a world patent right?

Exercise 3.6 - steps in the patent process - the national phase

Nizam's Institute made a PCT application on the ointment he invented. The international search report disclosed an earlier German patent that looked like it was relevant. The Institute requested an international preliminary examination under the PCT system. This resulted in a clear examination report. This reassured the Institute's financial backers who decided to support patent applications in each country possible. This includes Australia, so the application enters the national phase in Australia.

(i) What steps will be followed in the Australian patent process?

(ii) The Australian application goes through the examination and opposition process, with some amendments to deal with the German prior art. An Australian patent is then issued. Nizam's boss asks him whether this will give the Institute patent rights it can enforce in Japan and the US, where a competing product imitating the ointment has been put on the market. His boss knows that these countries are all members of the same international patent conventions, such as the PCT, the Paris Convention and TRIPS, and assumes this means the Australian patent can be enforced . What should Nizam tell his boss?

Module 3 Group Exercises: United States Patent 6,139,898

US006139898A

United States Patent [19]

Meyer et al.

[11] **Patent Number: 6,139,898**

[45] **Date of Patent: Oct. 31, 2000**

[54] **FULL MOISTURE SHELF STABLE RICE PRODUCT**

[75] Inventors: **Paul Philipp Meyer**, Benglen; **Peter Jonas Halden**, Seuzach, both of Switzerland; **Göran Jaelminger**, Helsingborg; **Eva Ehrenberg**, Löddeköpinge, both of Sweden

[73] Assignee: **Nestec S.A.**, Vevey, Switzerland

[21] Appl. No.: **09/280,042**

[22] Filed: **Mar. 26, 1999**

[30] **Foreign Application Priority Data**

Mar. 27, 1998 [EP] European Pat. Off. 98200964

[51] **Int. Cl.**[7] **A23L 1/168**; A23L 1/172; A23L 1/18; A23B 4/03

[52] **U.S. Cl.** **426/618**; 426/114; 426/268; 426/303; 426/309; 426/310; 426/316; 426/399; 426/407; 426/509

[58] **Field of Search** 426/113, 114, 426/293, 303, 309, 316, 310, 618, 629, 654, 399, 407, 509, 510, 268

[56] **References Cited**

U.S. PATENT DOCUMENTS

2,195,165	3/1940	Choppin et al.	53/21
4,649,055	3/1987	Kohlwey	426/489
4,902,528	2/1990	Groesbeck et al.	426/625
5,089,281	2/1992	Baz et al.	426/461
5,293,814	3/1994	Vorwerck et al.	99/355
5,562,938	10/1996	Lee et al.	426/106
5,702,745	12/1997	Yang et al.	426/242
5,997,930	12/1999	Kendall et al.	426/460

FOREIGN PATENT DOCUMENTS

0 322 996	7/1989	European Pat. Off. .
2 130 906	10/1972	France .
2 502 907	3/1982	France .
52-122645	10/1977	Japan .
3087153	4/1991	Japan .
990063	4/1965	United Kingdom .

OTHER PUBLICATIONS

S.L. Bor: "Rice: Production and Utilization" 1980. AVI, USA XPO002068550, pp. 566–574, 593–597.

Primary Examiner—Nina Bhat
Attorney, Agent, or Firm—Pennie & Edmonds LLP

[57] **ABSTRACT**

A full moisture shelf stable rice product, which comprises a cooked or precooked whole grain rice having a dry matter content of from about 30% to about 55% by weight, an acid in amount effective to obtain a pH of about 3.5 to about 4.5, and an oil in an amount sufficient to coat the surface of the rice.

16 Claims, No Drawings

FULL MOISTURE SHELF STABLE RICE PRODUCT

TECHNICAL FIELD

The present invention relates to a rice product consisting of cooked or precooked whole grain rice having a long shelf life.

BACKGROUND ART

JP52122645 (DAINIPPON PRINTING) discloses the preparation of sterilized boiled rice, by filling a container with rice and 40% to 55% water in heat-resistant pouches or cans, sealing them tightly, and cooking and sterilizing them simultaneously by heating with rotating.

FR2502907 (BUITONI) discloses the production of precooked solid food, especially pasta products and rice, by precooking the food in acidulated water, cooling in acidulated water, draining off excess water, oiling, insertion into flexible containers and heat sterilizing the sealed containers.

JP3087153 (ASAHI CHEM IND) discloses the preparation of packaged processed rice with good preservability, by heating rice, controlling its acidity to within a pH range of 3.5 to 6 and its moisture content to within 20% to 30%, and preventing grains from aggregation by light crushing.

SUMMARY OF THE INVENTION

The present invention relates to a full moisture shelf stable whole grain rice having outstanding organoleptical quality which is not intended to be fully cooked by the consumer but, on the contrary, is intended to be consumed after unpacking and simple heating or short cooking.

In addition, the present invention provides a process for manufacturing a full moisture shelf stable whole grain rice of outstanding quality which is intended to be consumed after unpacking and simple heating or short cooking.

The full moisture shelf stable rice product according to the present invention has a pH range of about 3.5 to about 4.5, preferably about 3.8 to about 4.3, and comprises a cooked or precooked whole grain rice having a dry matter content of from about 30% to about 55% by weight. The rice product also contains an acid in amount effective to obtain a pH of about 3.5 to about 4.5, and an oil in an amount sufficient to coat the surface of the rice.

The process for manufacturing a full moisture shelf stable rice product according to the present invention comprises the steps of water soaking whole grain rice, portioning, blanching, water cooling, dipping into acidified water, oiling, packaging, and in pack pasteurising of the rice product.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the present rice product, the whole grain rice may be of any commercially available rice kind or variety. It may especially be a short grain rice such as Italian Camolino rice, a parboiled white long grain rice, a Thai long grain fragrant rice or a Basmati rice.

The acid may be any food grade acid, especially lactic acid, phosphoric acid, citric acid, or Glucono-delta-lactone.

The oil may be any vegetable oil, and is advantageously present in an amount of from about 0.5% to about 5% by weight of the cooked or precooked grain. The oil may especially be peanut oil, rapeseed oil, sunflower oil, palm oil, corn oil, palm olein or mixtures thereof. About 0.5% to about 2% of emulsifiers, in percent by weight of the oil, and especially a monoglyceride or mixtures of monoglycerides, may advantageously be added to the oil to assist in coating the surface of the rice grains.

To implement the present process, one can start with a raw material in the form of a commercially available whole grain rice typically having a dry matter content of from about 86% to about 91%.

This rice may be soaked at a ratio of about one part of rice to about one to four parts of water at about 30° C. to 60° C. for about 30 minutes to about 5 hours. The purpose of the soaking step is to minimize starch losses and to open up the structure of the grain in order to facilitate the heat transfer as well as the water uptake during the blanching step.

During the soaking step, the water uptake may be such that the rice attains a dry matter content of from about 65% to about 72%.

The step of portioning, namely dividing or dosing the rice into portions which then will be individually packaged, may be carried out at any stage after the soaking step and before the packaging step.

The soaked rice may be blanched by steaming or by steaming and hot water-spraying, especially hot acid water-spraying, the purpose of water-spraying during steaming being to minimise starch losses during blanching.

The blanching step may be carried out at about 95° C. to about 100° C. for about 1 minute to about 10 minutes, while steaming with steam at about 98° C. to about 100° C. and spraying water at about 95° C. to about 98° C., especially water having a pH range of from about 3.5 to about 5. Spraying acidified water during blanching achieves a whiter color of the rice.

During the blanching step, the water uptake may be such that the rice achieves a dry matter content of between about 35% to about 52%.

After the blanching step, the rice may be advantageously showered with a hot water spray. In other words, the rice may be passed under a shower of hot water, especially of water having a temperature of from about 60° C. to about 70° C., in order to loosen the individual grains which can be slightly sticky after having been steamed.

Water cooling may be carried out in a bath of water at ambient temperature, namely at a temperature of between about 18° C. to about 35° C., for about 30 seconds to about 2 minutes.

After water cooling, excess water may be drained off for about 30 seconds to about 2 minutes.

During the water cooling step, the blanching step may be stopped completely and the water uptake may be such that the rice has a dry matter content of between about 30% to about 55%.

After water cooling and possibly draining off excess water, the rice is dipped into acidified water in order to be acidified to a final pH which is within the range of about 3.5 to about 4.5. To this end, the rice may be dipped into a water containing from about 0.5% to about 2% of a food grade acid, especially lactic acid, phosphoric acid, citric acid, or Glucono-delta-lactone, at ambient temperature, especially at a temperature of from about 18° C. to about 35° C., for from about 50 seconds to about 250 seconds.

After this acidifying step, excess acidified water may be drained off for about 30 seconds to about 2 minutes.

During the acidifying step, there is very little further water uptake. The acidification of the rice appears to be mainly a result of osmotic equilibration.

The oiling step may be carried out so that the surface of the rice is coated with oil in an amount of from about 0.5% to about 5% by weight of the rice. In order that the oil is well distributed in very fine particles over the rice surface, about 0.5% to about 2% of emulsifiers, in percent by weight of the oil, may be added to the oil.

The oiling step may be carried out either before or during the packaging step. Preferably, the rice is packaged in a flexible pouch with a controlled volume of head space. To this end, the rice may be dosed into a vertical pouch after its bottom has been sealed and oil may be injected into the pouch before its top is sealed.

Eventually the packaged rice product is in pack pasteurized. This in pack pasteurizing step may be carried out using a steam medium, while maintaining the temperature in the center of the pouch at from about 80° C. to about 100° C. for from about 1 minute to about 80 minutes.

The pouches may then be cooled either for about 5 minutes to about 15 minutes in cold water containing a disinfectant, or for about 30 minutes to about 60 minutes by chilled air, at about 5° C. to about 15° C.

The present process may be implemented by means of normal equipment such as steeping unit, steam/water spraying blancher, water bath, shower and pasteurizing unit from the pasta or noodle industry.

The present process surprisingly provides a rice product having outstanding organoleptical properties, especially an outstanding texture, in view of the fact that it is not intended to be actually cooked again at the consumer's end but only heated up or cooked for a very short period after unpacking.

Heating up or quickly cooking the present rice product after unpacking may be carried out in a pan, in a microwave oven, or by pouring hot or boiling water onto it.

EXAMPLES

The rice product and the process according to the present invention are illustrated in the following Examples in which the percentages and parts are by weight unless otherwise stated.

Example 1

A precooked rice product having a long shelf life was made from a commercially available long grain Thai fragrant rice having a dry matter content of 89.5%.

The rice was soaked at a rate of one part of rice for three parts of soft water at 50° C. for 1 h. The water uptake during soaking was such that the rice had a dry matter content of from about 67.9%.

The rice was portioned or dosed in 84 g portions.

The rice was then blanched at about 98° C. for 6 minutes along a tunnel blancher in which steam injection means injected steam at 99° C. and water spraying means sprayed acidified water having a pH range of 4.0 to 4.5 and a temperature of 96 to 97° C.

During the blanching step, the water uptake was such that the rice had a dry matter content of 51.9%.

After the blanching step, the rice was water cooled in a bath of water at 20° C. for 45 seconds.

During the water cooling step, the water uptake was such that the rice had a dry matter content of 43.3%.

After water cooling, excess water was drained off for 60 seconds.

The rice was then dipped into water containing 0.8% lactic acid and having a temperature of 30° C., for 105 seconds.

During the acidifying step, the water uptake was such that the rice had a dry matter content of 42.0%.

After the acidifying step, excess acidified water was drained off for 60 seconds.

After the acidifying step the rice had a pH of 3.9.

The rice portions then weighing about 140 g were dosed into vertical pouches after their bottoms had been sealed, and 1.5 g palm olein were injected into each pouch before their tops were sealed.

The rice was in pack pasteurized in steam at 97° C., the temperature in the center of the pouch reaching a temperature of 85° C. after 20 minutes and this temperature being hold for 10 minutes.

The pouches were then cooled for 10 minutes in water having a temperature of 10° C. and containing a disinfectant. The pouches were subsequently stored at 25° C.

The rice product could be prepared for consumption by unpacking and heating up.

The rice did not stick together. It had outstanding organoleptical properties, especially a texture similar to the texture of freshly cooked Thai fragrant rice.

Example 2

A precooked rice product having a long shelf life was made from a commercially available short grain Italian Camolino rice having a dry matter content of 86.7%.

The rice was soaked at a rate of one part of rice for three parts of soft water at 50° C. for 1 h. The water uptake during soaking was such that the rice had a dry matter content of from about 66.4%.

The rice was portioned or dosed in 89 g portions.

The rice was then blanched at about 98° C. for 6 minutes along a tunnel blancher in which steam injection means injected steam at 99° C. and water spraying means sprayed acidified water having a pH range of 4.0 to 4.5 and a temperature of 96 to 97° C.

During the blanching step, the water uptake was such that the rice had then a dry matter content of 43.4%.

After the blanching step, the rice was water cooled in a bath of water at 20° C. for 45 seconds.

During the water cooling step, the water uptake was such that the rice had a dry matter content of 41.4%.

After water cooling, excess water was drained off for 60 seconds.

The rice was then dipped into a water containing 0.8% lactic acid and having a temperature of 30° C., for 105 seconds.

During the acidifying step, the water uptake was such that the rice had a dry matter content of 41.2%.

After the acidifying step, excess acidified water was drained off for 60 seconds.

After the acidifying step the rice had a pH of 4.0.

The rice portions then weighing about 150 g were dosed into vertical pouches after their bottoms had been sealed, and 1.5 g palm olein were injected into each pouch before their tops were sealed.

The rice was in pack pasteurized in steam at 97° C., the temperature in the center of the pouch reaching a temperature of 85° C. after 20 minutes and this temperature being hold for 10 minutes.

The pouches were then cooled for 10 minutes in water having a temperature of 10° C. and containing a disinfectant. The pouches were subsequently stored at 25° C.

The rice product could be prepared for consumption by unpacking and heating up.

The rice did not stick together. It had outstanding organoleptical properties, especially a texture similar to the texture of freshly cooked Camolino rice.

What is claimed is:

1. A full moisture shelf stable rice product, which comprises a cooked or precooked whole grain rice having a dry matter content of from about 30% to about 55% by weight, an acid in amount effective to obtain a pH of about 3.5 to about 4.5, and an oil in an amount sufficient to coat the surface of the rice.

2. A rice product according to claim **1**, in which the pH is about 3.8 to about 4.3.

3. A rice product according to claim **1**, in which the acid is a food grade acid.

4. A rice product according to claim **3**, in which the food grade acid is lactic acid, phosphoric acid, citric acid, or Glucono-delta-lactone.

5. A rice product according to claim **1**, which comprises about 0.5% to about 5% of the oil, in percent by weight of the cooked or precooked grain.

6. A rice product according to claim **1**, in which the oil is a vegetable oil.

7. A rice product according to claim **6**, in which the oil is peanut oil, rapeseed oil, sunflower oil, palm oil, corn oil, palm olein, or mixtures thereof.

8. A process of manufacturing a full moisture shelf stable rice product comprising the steps of: soaking whole grain rice in water, portioning the rice into predetermined amounts, blanching the portioned rice, cooling the blanched rice to a predetermined temperature with water, contacting the rice with acidified water to impart a pH of between about 3.5 and about 4.5 so that the rice has a dry matter content of from about 30% to about 55% by weight, treating the rice with an oil in an amount effective to coat the surface of the rice and form a rice product, packaging the rice product in a package, and treating the packages under conditions effective to achieve pasteurization of the rice product.

9. The process of claim **8**, wherein the rice is soaked at a ratio of about one part of rice for about one to four parts of water at about 30° C. to about 60° C. for about 30 minutes to about 5 hours.

10. The process of claim **8**, wherein the blanching step is carried out at about 95° C. to about 100° C. for about 1 minute to about 10 minutes, while steaming with steam at about 98° C. to about 100° C. and spraying water at about 95° C. to about 98° C.

11. The process of claim **10**, wherein the spraying water has a pH of about 3.5 to about 5.

12. The process of claim **8**, wherein the acidified water contains about 0.5% to about 2% acid.

13. The process of claim **12**, wherein the acid in the acidified water is lactic acid, phosphoric acid, citric acid, or Glucono-delta-lactone.

14. The process of claim **8**, wherein the rice is dipped into the acidified water for from about 50 seconds to about 250 seconds to achieve the recited pH.

15. The process of claim **14**, wherein the temperature of the acidified water is about 18° C. to about 35° C.

16. The process of claim **15**, wherein the rice is in pack pasteurized using steam and maintaining the temperature in the center of the pouch at from about 80° C. to about 100° C. for from about 1 minute to 80 minutes.

* * * * *

FOREIGN AFFAIRS AND TRADE

AUSTRALIA

AusAID the Australian Government's overseas aid program

Module Four

Searching Patent Databases

Intellectual Property and Biotechnology
A Training Handbook

Contents: Module Four

4.1 Objectives for Module Four

By the end of this Module you should have an understanding of

- the potential uses of searching patent information
- the reasons for an internationally harmonised system of patent classification
- the international patent classification system
- how to prepare a search strategy
- the main sources of information relating to patent
- the key tools and techniques for searching databases, and
- how to conduct a search of a database for patent information.

4.2 How Can Patent Information Help You?

A key requirement for the grant of a patent is that details about how to practise an invention are *disclosed* (that is, made public) in return for patent rights for a limited period of time. A patent operates as a deal between society and the inventor, which requires the inventor to describe the invention fully, so that anyone with general technical skills can put it into effect. This means that each patent document serves as a specific, focussed text-book on a particular state-of-the-art development in technology. In almost all countries, patent applications are published 18 months after the effective application date of the patent, well before the actual patent is granted or enforceable patent rights exist, meaning that patent information is especially rich in newly-developed technologies. Often, the technological information published in patent documents is not published in any other form, and rarely is it so accessible as through the patent information system.

The term of a patent is generally no more than 20 years (many patents lapse before 20 years expires, as normally an annual fee must be paid to keep a patent in force, and in a significant number of cases this is not paid for the full 20 years). When the term of patent protection finishes, the invention is in the public domain and can be used freely without permission from the patent owner and without payment to them, for the wider benefit of the community. Even while a patent is still in force, many countries allow for exceptions to patent rights for activities such as research and education – so that a patented technology can be used by research or educational institutions for limited non-commercial purposes, even while the patent is still in force. (The exact scope of such exceptions varies from one country to another, and should be checked carefully with a legal advisor).

The legal scope of a given patent only applies in the jurisdiction where the patent is granted – it does not give any rights in other countries. For example, say you work for a pharmaceutical company in Indonesia, and hear of a new patented technology for synthesizing insulin. You might find through patent searches that the technology is only protected by patents in the US, Japan, Europe, and Canada, and that national patents are not in force elsewhere. You would be legally entitled to use this technology without limitations in Indonesia, and could export the product to any other country (such as China or Australia) where no patents were in force. This would mean that you have no legal limitations on the use of the patented technology in your country (and in any export markets where there is no patent in force). The patent documentation relating to the foreign patents must have, by law, sufficient information for someone with general technical skills in the area to make the technology work. As a result, the patent information system can serve as an effective form of technology transfer for technologies, and as a practical aid to implementing new technologies. See *Module Two: Biotechnology and Intellectual Property* for further information about the legal requirements for the grant of a patent.

It is estimated that over 40 million patent documents have been published throughout the world, and that over 1 million new patent documents have been published each year for the past ten years. For instance, in the week of 10th May 2001, WIPO published 2178 new patent applications, and its Intellectual Property Digital Library (http://ipdl.wipo.int/) makes these immediately available on the internet. As an example, one of these applications, number WO 99/52503, discloses the following technology:

RNA cancer vaccines and methods for their use are described. The vaccines are comprised of viral liposomes comprising nucleic acid, preferably RNA, encoding a tumor-associated antigen. The viral liposomes may be formed by the fusion of HVJ reagents with non-viral reagents. The vaccine may be administered subcutaneously, intradermally, intramuscularly or into an organ. The vaccine may be administered to induce a host normal cell to express the tumor-associated antigen.

There is a huge amount of patent information available for you to search. Searching through patent information was, until recently, an expensive, difficult and time-consuming process. But recent developments in information technology – particularly the dissemination of relatively cheap PCs and the increasing ease of access to the Internet – have dramatically improved the possibilities for making use of patent information. It is now well within the reach of anyone with a PC and a reasonable internet connection to gain access to up-to-date patent information in any field of technology at no cost. (Some more sophisticated forms of patent searching still require the use of commercial information services.)

Patent information is obviously not the only source of technological information, or information relevant to research and development. Scientific journals, research publications, company reports, internet databases are all potentially very important, both to find out about technology and to examine whether a particular patent or patent application is valid. The particular benefits of patent documentation include:

- Patent documents appear in a common, easily searchable format, which is increasingly harmonised internationally;
- They have strong, easy to use cross-referencing between documents;
- They describe inventions in a way that is aimed at facilitating their reproduction in practice;
- They cover material which is, by definition, genuinely new and not earlier available to the public;
- Their subject matter is almost universally categorised by a single international classification system; and
- Access to much of the documentation is free of charge.

Patent information is valuable for a host of purposes. This can range from a major study on technological developments in a particular area (e.g. the history and current status of research into gene therapy), or a very specific single enquiry (e.g. is your competitor's patent still in force in Singapore?) The strategies and methods used for searching patent information therefore vary widely, depending on what the information is to be used for. Following are descriptions of some of the main uses of patent information.

State-of-the-art search, or technology survey

This is a search used in planning commercial or research activities, to determine the state of existing technology – there are many examples of cases where 'new' products are developed or research programs are undertaken at enormous expense, only to be met with the discovery that the problem had already been solved before the project commenced, and was the solution was freely available in patent information.

Often the existing solution in the patent documentation will be free for you to use, as there will not be a patent in force in your country; in other cases, even if the patent is in force, you can use the patent document to contact the owner of the technology who may well be interested in a commercial or research partnership with you – normally much less expensive than it would cost you to 'reinvent the wheel.'

Quite apart from the specific invention claimed in the patent, the descriptive material in patent documents also contains potentially useful information and references to the field of technology that existed prior to the claimed invention.

Examples of state of the art searches include:

- what pharmaceutical or industrial uses have been found for eucalyptus oil?
- what technologies have been developed for processing palm oil?

Technological updates

This is a search used to learn about emerging technologies and new developments. Most patent information is published 18 months from its effective application date. Patents are legally invalid if they are not novel at the application date, meaning that the effective application date normally predates any publication or public use or exploitation of the invention. This means that patent information can often be more up to date than general scientific and technical literature, especially when it is technology generated by private companies (which may not be otherwise published at all). This is a particular feature of biotechnology innovation, much of which is driven by private sector research and development, making patent information a vital source of up to date information.

Examples of technological update searches include:

- what recent progress has been made in developing a vaccine for malaria?
- what new techniques in genetic engineering are currently under development?

Infringement searches: assessing scope of existing intellectual property rights

Many patent searches are made to anticipate and avoid conflict with existing intellectual property rights. The first experience a business enterprise has with the intellectual property system can be very negative: they receive a demand from someone else, normally a competitor, claiming that they are infringing IPRs, and requesting that they stop, with a threat of legal action – often called a 'cease-and-desist letter.' This can be very expensive and harmful for a business. It can lead to the abandonment of research projects, or the launch of a new product, and potentially even the failure of a business, as well as expensive claims for damages.

Hence it is good practice to undertake a search of existing IPRs to determine to what extent they might limit your action – your 'freedom to operate.' Unlike the technology searches described earlier, the focus of this kind of search is basically legal: what IPRs exist that might be enforced against you. This makes the search strategy fundamentally different: you are not looking for the kind of technological information that is contained in the patent disclosure, but rather for patent claims that might conflict with your activity. So even if the patent document describes research in your general area of technology which overlaps with your own, it may only be of concern if

If you were only interested in the domestic market in, say, Thailand, or only wanted to conduct your business in the ASEAN region, for this kind of search you would not need to search US or European patents, because they have no legal effect on you and your choice of technology. Equally, you would not need to consider patents that had lapsed, e.g. through failure to pay renewal fees (although it is normally possible for such patents to be reinstated within a limited period, so this would need to be factored into the search).

Essentially, this kind of patent search is more limited in scope and is generally looking only for those patents which:

- have legal effect in the actual countries you are operating in;
- have claims that cover the scope of your proposed operations; and
- have not lapsed or expired and are still in force, or are live applications under consideration.

Patentability searches

If you are developing a new technology and wish to seek financial support for it to be commercialised, one of the first questions you might be asked is – can it be patented? You then need to know what existing technologies have already been the subject of patent

documents – either in the claims or in the description. Patent documents and other documents can both be relevant – from the point of view of patentability, the chief issue is whether the information was available to the public in any format. So the search for relevant patents is very important, but cannot be relied upon as the only source of information. A patentability search is a vital step in planning research and the further development of your technology, and in creating an intellectual property protection strategy.

For example, say your laboratory developed a new technology ('process X') for isolating a particular enzyme ('enzyme Y'), which could be useful in treating a medical condition. Your researchers believe that both process X and the isolated enzyme Y are completely new, and are keen to gain a patent that might help fund further research programs. Your development and commercialisation strategy will depend on whether this invention can be patented, and which elements of the invention can be patented.

A search might turn up an earlier patent document (or an article in a scientific journal) that reveals a very similar method to the 'process X' technique – the technique that was independently developed by your laboratory – but it may not mention the possibility of isolating the particular enzyme Y. That earlier document is part of the 'prior art' – the background of pre-existing published technology that is relevant to your invention. You will need to analyse this piece of prior art very closely to make the judgement whether your new process is likely to be eligible for a patent. Perhaps the specific way you used process X to isolate enzyme Y was in itself inventive, because there were particular problems you had to overcome. Whether or not it is judged inventive will be determined with reference to the existing common general knowledge in the field at the time you filed your patent – and this will partly be determined by checking on existing patents already published at that time.

Sometimes the patent search brings particularly bad news – not only is your invention not novel, and so not eligible for a patent, but in pursuing the development of the planned new product, you would actually be infringement of existing patent rights. Having this news does at least help avoid unnecessary expense on unsuccessful patent applications and commercialisation activities, and could be used to refocus your plans.

A patentability search also involves searching non-patent literature – typically, this would include databases and scientific journals, but can also cover specific information resources such as records of traditional knowledge. Generally speaking, you have an interest in having the search cover as diverse a range of information as your resources allow. No search can ever be fully universal, and there is always a risk, however slight, of a relevant document turning up later from an unexpected source.

4.3 How is patent information classified?

Unless you are searching for something specific – such as any patent in the name of XYZ Company, or any patented invention invented by a particular person – then the search process is likely to focus on a particular area or areas of technology. To make the search feasible, it is necessary to narrow down the range of documents you look through- typically this is done by date and above all by reference to subject matter. Searching by subject matter can involve the use of key words and technology categories. For instance, you might be interested in fertilizers and methods for applying fertilizers. You might try a word search using the word 'fertilizers,' but you would then miss out on many patents for fertilising products or processes which referenced the particular chemicals concerned, or used a similar word such as 'growth stimulant.' All published patent information is classed according to its field of technology, under a classification system. Patent offices have moved towards harmonisation in this field, with the establishment of the International Patent Classification (IPC) system. This allows for effective and efficient patent searching throughout the world.

To Assist Researchers to Search Patent Information

A uniform international system of classification for technology is necessary to assist researchers. As noted above, there are many ways that searching patent information can be of assistance to researchers. If there were no internationally harmonised system of classification for technology, it would be very difficult and time-consuming to do effective searches of patent information. In some cases effective searching would even be impossible without an internationally harmonised system of classification for technology.

To Assist Patent Examiners to Search "Prior Art"

An internationally harmonised system of classification for technology is also necessary to assist patent examiners in patent offices to do a "prior art" search when examining an invention in a patent application. "Prior art" in patent law refers to the published documents and common general knowledge in the field of technology related to the invention before the priority date of the patent application. Prior art documents can be published anywhere in the world

In *Module Two: Biotechnology and Intellectual Property* the legal requirements for a patent to be granted are set out. Those requirements are that an invention must be novel, involve an inventive step and be capable of industrial application. *Module Three: Reading a Biotechnology Patent and the Patent Process* sets out the administrative steps in the patent process. As noted in that Module, a key step in the patent process is the examination of a patent application by a patent examiner to see if the invention satisfies the legal requirements for patenting. As part of the examination of a patent application, a patent examiner must conduct a prior art search to make sure that the claimed invention is novel and involves an inventive step. Obviously an internationally harmonised system of classification for technology is crucial to enable patent examiners to conduct an effective prior art search.

How does the IPC work?

As noted in *Module One: Introduction to Intellectual Property*, the Strasbourg Agreement concerning the International Patent Classification (1971) sets up the International Patent Classification (IPC).

The purpose of the IPC is to classify technology in a uniform way to make it easier to search patent documents using the IPC system of classification. As noted above, a key part of the patent process is a prior art search of published documents to find out if an invention satisfies the legal tests for patenting such as novelty and inventive step. The IPC provides a uniform system to classify technology to enable effective prior art searching of published documents. Without the IPC searching for prior art would be complex and the results of searches would be unreliable.

The seventh edition of the IPC, which entered into force on 1 January 2000, classifies technology into eight sections with approximately 69 000 subgroups. The seventh edition of the IPC is reproduced in 10 bound volumes containing more than 1,700 pages. It is available on line at: http://classifications.wipo.int/fulltext/new_ipc/index.htm

The eight sections in the IPC are as follows:

A Human Necessities
B Performing Operations; Transporting
C Chemistry; Metallurgy
D Textiles; Paper
E Fixed Constructions
F Mechanical Engineering; Lighting; Heating; Weapons; Blasting
G Physics
H Electricity

The IPC is used by patent offices in more than 80 countries and the secretariat of WIPO, which administers the PCT. According to WIPO, over the last 10 years the appropriate IPC symbols have been put on around 1 000 000 patent documents.

For example, if you were interested in new method and apparatus for spreading fertilizer and had in mind a specific application to superphosphate fertilizers, you could use the IPC to narrow down your search to particularly relevant subject matter. You could choose to look for patents about superphosphate fertilizers, and for patents about fertilizer distributors and methods of fertilizing. You would then locate the following classifications under the IPC system:

Section C – Chemistry; Metallurgy
Class C05 Fertilisers; Manufacture thereof
Subclass C05B phosphatic fertilisers
Main group 1/00 superphosphates, i.e. fertilisers produced by reacting rock or bone phosphates with sulfuric or phosphoric acid in such amounts and concentrations as to yield solid products directly
subgroup 1/02 superphosphates
subgroup 1/04 double-superphosphate; triple-superphosphate other fertilisers based essentially on monocalcium phosphate
subgroup 1/06 ammoniation of superphosphates
subgroup 1/10 apparatus for the manufacture of superphosphates

Section A – human necessities
Subsection - Agriculture
Class A01 agriculture; forestry; animal husbandry; hunting; trapping; fishing
Subclass A01C planting; sowing; fertilising
Main group 15/00 Fertiliser distributors
Main group 21/00 Methods of fertilising

You could then begin your search using the codes for the subclasses A01C and C05B. If this produced too many documents, you could use the further codes for the main groups or even subgroups you are interested in. So you could search with the codes:
A01C 15/00 and A01C 21/00
C05B 1/00 (or for a more focussed search, C05B 1/02 etc.)

The IPC is discussed further below under the heading "what are some approaches to searching databases?"

4.4 How do I develop a search strategy?

Given the huge amount of patent information available throughout the world you need to be strategic about how to approach your search. You should consider a range of factors when you develop a strategy to search databases. These factors include:

- the nature of invention, including the breadth of the claims, the field of technology to which your invention relates and the terminology used in the field;
- the aim of your search;
- how much time and money you have; and
- your skills in using the databases.

The Nature of Your Invention

In developing a search strategy you need to be aware of the nature of your invention. This means that you need to know the breadth of the claims over the invention in your patent application. You need to know the breadth of the field of technology to which your invention relates. You also need to have knowledge of the terminology used in that field of technology. These considerations will help you to do an effective search because they will help you to identify what you are looking for in your searches.

The Aim of Your Search

The aim of your search is another important consideration in developing a search strategy. You need to be clear about the aim of your search in order to do an effective search. At different stages of your research the searches that you do will have a different aim. These include the range of searches discussed above:

- patentability searches;
- state-of-the-art searches;
- infringement searches;
- validity searches; and
- right to use searches (which can also be called "freedom to operate" searches).

The potential of patent information for researchers and enterprises is only now beginning to be widely appreciated, partly because the costs and technical barriers to access have been greatly reduced. There are now many publications on searching techniques and strategies. For more information on "freedom to operate" please see *Module Eight: Researching and Intellectual Property Rights*.

It can be seen from the different aims of searching set out above that it is necessary to search for patent information at various stages throughout your research. Your combined intellectual property and research and development strategy should include searching patent information at three stages of your research. First, you may need to search even before the research program commences, as part of the research planning and setting objectives, to ensure that you are not undertaking research that has already been done (commonly described as 'reinventing the wheel'), or has resulted in failure. There are cases of large companies undertaking research programs only to discover that the same research had already been done and patented in the past – even by the same company. Search is also important when you think that you have developed a patentable invention, because you will need to check whether there is prior art that could interfere with your claim for a patent. And you may need to search patent documentation when planning to commercialise or publicly exploit a product based on your invention, to ensure you have freedom to operate.

The Time and Money You Have Available

The time and money you have available to conduct searches are other factors that you need to consider in developing a search strategy. You need to keep in mind that the use of commercial databases can be expensive and even the use of free databases can be time-consuming, particularly if you do not have specialist searching skills. The costs of using databases are usually outweighed by the benefits of the searches, particularly searches that are conducted to ensure freedom to operate. Having a strategy for searching databases will help you to ensure that the benefits of searching outweigh the costs.

Your Skills in Using the Databases

It is not always necessary to get specialist help to search a patent database, especially if you are mostly looking for relevant information rather than trying to find out whether there are any patents that could be a legal problem. Exercise 4.5 in this Module shows how you can search a patent database yourself. However, specialist help in searching databases is advisable, particularly in relation to prior art searches and searches conducted to ensure freedom to operate before you commercialise your invention. Searching databases in these circumstances requires specialist skills and is time consuming. Patent offices, patent attorneys and other commercial enterprises provide international searching services.

Sources of information

For most searches your strategy should take account of sources of information other than patent databases. A 'freedom to operate' search or a search for existing patent rights is, of course, limited to patent databases as such. But searches to check for the validity of a patent and to determine the current state of the art in a particular technology may need to include other non-patent databases (including a general internet search) and searching through scientific and technical journals, and other publications. A number of particular sources of information are listed at the end of this Module. As you gain experience and develop your searching skills, you should also try to learn more about all the various sources of information available in your particular area of interest, including patent databases, other on-line databases, and technical and scientific publications. Business or general news publications can also be relevant to determining novelty.

You should not rely only on the major patent offices' patent databases, and the patent material that is available on the internet – for many people working in the Asia-Pacific region, other national patent information resources could be even more important. In some cases, this information is available on the Internet, or through CD-ROM services, but in other cases, it may be necessary to search hard-copy documents in a patent office to find out what patent documents have been published in a particular country. The national patent office in question should be able to give you information on how to gain access to this information. (A links to a directory of national offices is provided at Section 4.8.)

4.5 What techniques are used to search patent databases?

There are four main approaches to searching databases for patent information. These four approaches are discussed below. They are:

- thread;
- keyword;
- IPC; and
- sequence.

Each of these tools and techniques for searching databases has advantages and limitations. With practice you will get to know which technique will be the most appropriate for your particular search. Exercise 4.5 at the end of this Module will give you practice in doing a search yourself and deciding which searching techniques to use.

Thread

The first approach to searching databases for patent information is called the "thread" approach. An advantage of the thread approach is that it is easy to use.

This approach is built on the relationship between the subject matter of patent documents. In the case of US patents for example, each database entry carries hyperlinks to other patent documents related to the first. These relationships may be through their having the same applicant or one document citing another. This means that once you have a single patent document related to your area of interest, you can easily locate others without needing to delve too deeply into the content of each document you uncover in order to identify another potentially relevant document.

The disadvantages of this approach are that:

1. You must already have one related document to use as a starting point. This means that you must first use another search tool to get that starting document. Examples of databases that permit thread searching are the United States Patent and Trademark Office (USPTO) databases (www.uspto.gov), the IBM patent server (www.delphion.com) and the European Patent Office Database (Espace) (www.ep.espacenet.com)
2. the only documents that can be found using this approach are those that refer to one another and are available in electronic form on the database you are interrogating. This means that many documents may remain undiscovered. For example a relevant but old US patent document may not be accessible via the USPTO database. Equally, an obscure foreign patent document may not have been found during the search that provides the basis for the links in the database and so will not be provided as a hypertext link.

There are a limited number of free sites for thread searching some of which are indicated above. There are also commercial sites such as STN Scisearch.

Keyword

A second approach to searching databases for patent information is the keyword approach.

Keyword searching locates documents related by Keyword, not by explicit reference to one another. The approach requires that you identify one or more keywords that describe the essential and distinguishing features of your invention and enter them into a search engine. The complexity of these search engines varies between databases ranges from simple combinations of words to complex search statements using booleans, wildcards and proximity operators. Typical Boolean operators include 'and,' 'or' and 'and not.' Wildcards include '*' for any string of characters, and '?' for any single character. Proximity operators include 'near.' There are several examples of the use of these operators later in this Module.

The selection of appropriate keywords is crucial when using the keyword approach to searching databases and is a highly skilled task. To conduct effective keyword searching you therefore need knowledge of the field, including knowledge of synonyms and jargon. You also need knowledge of the databases to understand and work with controlled language, operators, inconsistent abstracting and inconsistent search targets.

The advantages of this approach are that

1. it is far more rigorous and flexible than thread searching;
2. there are more databases available;
3. documents only have to have the same technical content rather than referencing one another;
4. both patent and non-patent literature databases are available for Keyword searching; and
5. it can be used to identify a starting document for Thread searching.

The disadvantages are that:

1. some technical knowledge of the field is required including jargon and synonyms;

2. some knowledge of how the search engine functions is necessary to produce reliable results. The more flexible and powerful the search engine used, the more knowledge and experience is required; and
3. knowledge of the relevant databases, including abstracting and controlled language, is necessary to produce a reliable result.

A variety of services are available. These include free services, publication specific services and commercial services.

Examples of free services are PubMed, IBM Patent Server and Patent Offices. Examples of publication specific services are EMBO Journal and Nature On-line. Commercial services include Derwent, STN, CA and Medline.

Internet search engines (e.g. *yahoo*, *altavista*, *google*) can be used to search for patent information. However, a drawback of such a search tool is that there is too broad a range of topics.

Journal or nation specific searches can be done. However, in contrast to the problems faced with using internet search engines, journal or nation specific searches produce only a limited search.

Commercial sites can be expensive if not used skilfully. Costs of commercial sites include the contact hours, search question costs, printing costs and the searcher's time.

International Patents Classification (IPC)

As noted above, the IPC is the common patents classification system, which is administered by WIPO. The IPC classification can therefore form the basis of a search of the patent literature and several databases may be searched using this classification. Most commercial patent databases permit searching on the IPC in conjunction with keyword and other provider specific search facilities. The IPC can therefore provide a broad 'first cut' of the available material which can be refined with keywords.

The advantages of using the IPC for searching are that it is:

1. specifically designed for patent literature;
2. regularly revised (every 5 years);
3. detailed and hierarchical, which makes it logical and relatively easy to understand;
4. internationally recognised; and
5. a classification system used in both commercial and government databases.

The disadvantages are that:

1. the IPC has insufficient subdivisions and most of the specific subdivisions are already full;
2. IPC revisions are slow and sometimes incomplete;
3. it is not specialised for biotechnology inventions;
4. classification into the IPC is not consistently applied in different Patent Offices;
5. use of the IPC for searching requires detailed understanding of technology and the IPC; and
6. the information classified into the IPC is, of course, limited to patent documents.

Gene/Protein Sequence

The Gene/Protein Sequence approach to searching identifies matching nucleic acid or protein even when the names differ. The approach requires the searcher to enter a search sequence and the search engine then identifies matching sequences.

The advantages of this approach are that:

1. it is possible to conduct both identity and homology searching;
2. identified sequences are often hyperlinked to Medline abstracts; and
3. it does not require a detailed knowledge of the technology to which the sequence relates to conduct a reliable search.

The disadvantages are that:

1. you need sequences in order to conduct the search;
2. to get the best results you need to understand how the search engine identifies the abstracts. This involves sophisticated statistical algorithms;
3. generally the search cannot be limited to a mode of action or species although a combined sequence and keyword search is available in DGene and Chemical Abstracts; and
4. access to Gene/Protein Sequence searching tools is only available through commercial suppliers.

Non-Patent databases include CA, ANGIS, SWISSPROT and GENEBANK. Patent databases include Dgene and Chemical Abstracts (CA).

Combination Techniques

It is important to recognise that inventions in any field are unique and it is unlikely that one searching tool or approach will satisfy all situations. Most professional searchers therefore search in a variety of ways and a variety of places depending on the invention and the technology to which it relates. This is especially true where the invention has several aspects. For example a new gene coding for a particular therapeutic compound may need to be searched as the gene sequence (sequence search), the compound (keyword / IPC search - eg Chemical Abstracts) and the pharmaceutical preparation (Keyword - eg Medline).

When setting out to conduct a search remain flexible in your approach and develop a search strategy that is tailored to your invention.

4.6 Examples of patent search databases

The following replicates the WIPO PCT database search within the WIPO Intellectual Property Digital Library (http://ipdl.wipo.int/en/search/pct/search2.html).

PCT Database Search Page

This page provides an advanced search interface to the PCT Database. A simplified search interface is available on the Structured Search Page or Simple Search Page.

Search: ❍ **All** ⊙ **Week of: 17.05.2001**

Sort Results: ❍ **Chronologically** ⊙ **By Relevance**

Presentation: Basic

Query:

Example: et/needle or et/syringe andnot (sew* or thread)

Search Reset

Display:

25 results at a time ☐ Show pages in separate window

Pub. No.	Title	Pub.Date	Int. Class	App.Num	First Inventor	First Applicant	Abstract	Image Small
		☐	☐	☐	☑	☑	☑	

The PCT database field codes include: ET English Title, IN Inventor Name, ABE English Abstract, PA Applicant Name, DP Publication Date, ANA Applicant Nationality, AN Application Number, RP Legal Rep. Name , AD Application Date, PD Priority Date, IC International Class, PCN Priority Country, MC Main International Class, DS Designated States, LGP Language of Pub.

Some examples of searching strings:

Applications with priority date between 1st January 1997 and 10th June 1999 concerning agriculture (IPC class A01)	PD/01.01.97->10.06.99 AND IC/A01
Applications for inventions by Chakravarty, Chakrabarty, Chakravarti or Chakrabarti published between 1st May 2000 and 17th May 2001	(IN/Chakravart* or Chakrabart*) AND DP/01-05-2000->17-5-2001
All applications in the name of Mexican nationals which designate Viet Nam	ANA/MX AND DS/VN
All applications with *fertiliser, fertilizer, fertilizing, fertilising, fertilization*, *fertilisation* and *fertility* in the title or abstract	ET/fert* or ABE/fert*
All the above applications but without the word *egg*	ET/fert* or ABE/fert* ANDNOT ET/egg ANDNOT ABE/egg
The word 'light' close to 'sensitive,' 'sensor,' 'sense' or 'sensing'	light NEAR sens*

The following replicates a patent search page on the USPTO web site

US PATENT & TRADEMARK OFFICE

PATENT FULL TEXT AND IMAGE DATABASE

Home | Boolean | Manual | Number | Help

View Shopping Cart

Data current through 05/22/2001

Query [Help]

Example: **ttl/needle or ttl/syringe andnot (sew or thread$)**

Select Years [Help]

Examples of search codes:

PN : Patent Number; IN : Inventor Name; ISD : Issue Date; TTL : Title; ABST : Abstract; ICN : Inventor Country; ACLM : Claim(s); LREP : Attorney or Agent; AN : Assignee Name; CCL : US Classification; ICL : International Classification; APN : Application Serial Number; ACN : Assignee Country; APD : Application Date; EXP : Primary Examiner; PARN : Related US App. Data; REF : US References; FREF : Foreign References; PRIR : Foreign Priority; PCT : PCT Information; APT: Application Type (e.g. 1 = Utility or standard patent, 6 = Plant patent), SPEC: Description/Specification

Examples of searches:

To search for:	*try the search string:*
joint inventions by Boyer and Cohen:	IN/(boyer AND cohen)
inventions by Boyer and not by Cohen:	IN/(boyer ANDNOT cohen)
patents in the name of Genentech or Eli Lilly:	AN/(Genentech OR “Eli Lilly”)
patents for inventions by Thai inventors:	ICN/TH
plant patents concerning bananas:	APT/6 AND (TTL/banana OR ABST/banana)

Patent documentation and INID codes

Patent documents generally identify data fields by reference to two-digit codes, known as INID codes. "INID" is an acronym for "Internationally agreed Numbers for the Identification of (bibliographic) Data." You will see them on any of the patent documents or bibliographic data shown in this module - please see the following data extracts from WIPO PCT publications. Some of the important codes are

(10) Identification of the patent, SPC or patent document
(11) Number of the patent, SPC or patent document
(12) Plain language designation of the kind of document
(13) Kind-of-document code according to WIPO Standard ST.16
A1 Published with international search report
A2 Published without international search report and to be republished upon receipt of that report
A3 Subsequent publication of the international search report together with a revised version of the front page of the pamphlet
(20) Data concerning the application for a patent or SPC
(21) Number(s) assigned to the application(s),
(22) Date(s) of filing the application(s)
(23) Other date(s), including date of filing complete specification following provisional specification and date of exhibition
(24) Date from which industrial property rights may have effect
(25) Language in which the published application was originally filed
(26) Language in which the application is published
(30) Data relating to priority under the Paris Convention
(31) Number(s) assigned to priority application(s)
(32) Date(s) of filing of priority application(s)
(34) For priority filings under regional or international arrangements, the WIPO Standard ST.3 code identifying at least one country party to the Paris Convention for which the regional or international application was made
(40) Date(s) of making available to the public
(41) Date of making available to the public by viewing, or copying on request, an unexamined patent document, on which no grant has taken place on or before the said date
(42) Date of making available to the public by viewing, or copying on request, an examined patent document, on which no grant has taken place on or before the said date
(43) Date of making available to the public by printing or similar process of an unexamined patent document, on which no grant has taken place on or before the said date
(44) Date of making available to the public by printing or similar process of an examined patent document, on which no grant or only a provisional grant has taken place on or before the said date
(45) Date of making available to the public by printing or similar process of a patent document on which grant has taken place on or before the said date
(46) Date of making available to the public the claim(s) only of a patent document
(47) Date of making available to the public by viewing, or copying on request, a patent document on which grant has taken place on or before the said date
(48) Date of issuance of a corrected patent document
(50) Technical information
(51) International Patent Classification
(52) Domestic or national classification
(54) Title of the invention
(56) List of prior art documents, if separate from descriptive text
(57) Abstract or claim
(58) Field of search
(61) Related by addition to earlier application or grant <country> <number> <date>
(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application <country> <number> <date>
(71) Applicant(s), including indications in square brackets of [State of nationality/State of residence]
(72) Inventor(s) (74) Agent(s)/Common representative
(75) Inventor(s)/Applicant(s) (for US only), including indications in square brackets of [State of nationality/State of residence]
(81) Designated States (national) (84) Designated States (regional)

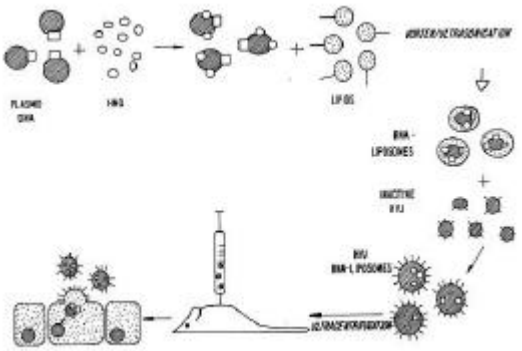
Examples of patent information from the WIPO PCT database

Note the use of INID codes

PUBLISHED INTERNATIONAL APPLICATION

(11) WO 99/52503
(13) A3
(21) PCT/US99/07488
(22) 05 April 1999 (05.04.1999)
(25) ENG
(26) ENG
(31) 09/061,794
(32) 16 April 1998 (16.04.1998)
(33) US
(43) 21 October 1999 (21.10.1999)
(51) 6 A61K 9/127, 39/00
(54) RNA CANCER VACCINE AND METHODS FOR ITS USE
(71) JOHN WAYNE CANCER INSTITUTE 2200 Santa Monica Boulevard, Santa Monica, CA 90404; (US). [US/US].
(72) HOON, Dave Apartment 301, 1911 Malcolm Avenue, Los Angeles, CA 90025; (US).
KANEDA, Yasufumi Osaka Univ., Institute for Molecular and Cellular biology, Div. of Cellular Genetics, Suita Osaka 565, 1-3, Yamada-Oka, Osaka 565; (JP).
(74) SHUSTER, Michael McCutchen, Doyle, Brown & Enersen, LLP, 3 Embarcadero Center, San Francisco, CA 94111; (US).
(81) AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW ; AP (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW); EA (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM); EP (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE); OA (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG)

Abstract: RNA cancer vaccines and methods for their use are described. The vaccines are comprised of viral liposomes comprising nucleic acid, preferably RNA, encoding a tumor-associated antigen. The viral liposomes may be formed by the fusion of HVJ reagents with nonviral reagents. The vaccine may be administered subcutaneously, intradermally, intramuscularly or into an organ. The vaccine may be administered to induce a host normal cell to express the tumor associated antigen.



PUBLISHED INTERNATIONAL APPLICATION

(11) WO 00/61067
(13) A3
(21) PCT/FR00/00938
(22) 12 April 2000 (12.04.2000)
(25) FRE
(26) FRE
(31) 99/04610
(32) 13 April 1999
(33) FR
(31) 99/16633
(32) 29 December 1999
(33) FR
(43) 19 October 2000 (19.10.2000)
(51) 7 A61K 39/21, C07K 14/16

(54) ANTI-HIV 1 VACCINE COMPRISING THE ENTIRE OR PART OF THE TAT HIV-1 PROTEIN

(71) CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE (CNRS) 3, rue Michel-Ange, F-75794 Paris Cedex 16; (FR). [FR/FR].(for all designated States except US)

(72)(75) LORET, Erwann 1, Boulevard des Iles d'Or, F-13009 Marseille; (FR) [FR/FR].

(74) MARTIN, Jean-Jacques Cabinet Regimbeau, 20, rue de Chazelles, F-75847 Paris Cedex 17; (FR).

(81) AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW; AP (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW); EA (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM); EP (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE); OA (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG)

No Image Available.

Abstract: The invention relates to an anti HIV 1 vaccine comprising the entire or part of the Tat HIV 1 protein, in addition to the identification of said protein in individuals affected by HIV. The Tat protein is a protein of the HIV1 Oyi variant.

4.7 List of Key Patent Databases

Some government patent databases available on the Internet:

Australia	http://www.ipaustralia.gov.au/patents/P_srch.htm
Brazil	http://www.inpi.gov.br/pesq_patentes/patentes.htm
Canada	http://patents1.ic.gc.ca/intro-e.html
European Patent Office	http://ep.espacenet.com/
France	http://www.inpi.fr/brevet/html/rechbrev.htm
Germany	http://www.dpma.de/suche/suche.html
Japan	http://www.ipdl.jpo.go.jp/homepg_e.ipdl
Korea	http://www.kipo.go.kr/ehtml/eLikIndex05.html
New Zealand	http://www.iponz.govt.nz/search/cad/dbssiten.main
Thailand	http://www.ipic.moc.go.th/
Trilateral Database	http://www.uspto.gov/web/tws/sh.htm
United Kingdom	http://www.patent.gov.uk/patent/dbase/index.htm
United States of America	http://www.uspto.gov/patft/index.html (Patents)

Directories of national patent administrations:

APEC economies	http://www.apecsec.org.sg/ipr/ipr.html
World-wide index	http://www.wipo.int/news/en/links/addresses/ip/index.html

Particular subject matter and commercial databases

US DNA patents	www.genomic.org
US agricultural patents	www.nal.usda.gov/bic/biotech_patents/
Pharmaceutical patents	www.current-patents.com
US chemical patents	Casweb.cas.org/chempatplus/
Biotechnology Patents	http://www.inform.umd.edu/EdRes/Topic/AgrEnv/Biotech/BiotechPatents
Sunsite's patent search	http://sunsite.unc.edu
Delphion patent server	http://www.delphion.com
Agriculture biotechnology	www.cambiaIP.org

4.8 Summary - Module Four

How can patent information help you?

- avoid 'reinventing the wheel';
- learn about emerging technologies before they appear in the journals and the market place;
- enhance the prospects for obtaining effective patent, trademark and design protection;
- avoid unnecessary expense on unsuccessful patent, trademark and design applications;
- monitor competitors' new product developments;
- obtain information about competitors' businesses; and
- anticipate and avoid conflict with competitors' intellectual property rights.

Why is a harmonised system of patent classification necessary?

- to assist researchers to search patent information; and
- to assist patent examiners search for "prior art".

How does the International Patent Classification (IPC) work?

- the Strasbourg Agreement Concerning the International Patent Classification, 1971 (IPC) sets up the IPC which is a structured, uniform classification of technological subject matter, to make it easier to search patent documents according to subject matter.

What factors should you consider in developing a search strategy?

Be strategic about searching patent information to ensure your searches are effective. Before you search you need to consider:

- the nature of your invention, including the breadth of the claims, the field of technology to which your invention relates and the terminology used in the field;
- the aim of your search;
- how much time and money you have; and
- your skills in using the databases.

What are main sources of information about patents?

- databases: WIPO IP Digital Library (publications of PCT applications), national patent office databases such as the USPTO database, and commercial databases such as Medline and Derwent, and

What are some approaches to searching databases?

- thread technique
- keyword
- IPC, and
- sequence.

4.9 Group Exercises – Module Four

Module Four provides information about searching databases for patent information. Please discuss Module Four with your fellow participants and prepare answers to the following questions.

Exercise 4.1 - benefits from searching databases

What benefit can researchers get from searching databases?

Exercise 4.2 - patent classification system

What is the name of the patent classification system used throughout the world? Why is an international system of classification of patents so important?

Exercise 4.3 - factors to consider in developing a strategy for searching patent databases

What factors should you think about before you start searching databases?

Exercise 4.4 - searching tools

What are the names of 4 different searching tools? When would you use each of the tools?

Exercise 4.5 - practical exercise

For this exercise, you will need access to internet facilities to enable you to do your own search of biotechnology patents. This searching exercise will provide you with an opportunity to locate technical information that is relevant to your research or policy interests. You will be able to put into practice the information we discussed in Module 4 such as:

- the issues to consider in developing a search strategy
- the different approaches to searching that are available to researchers and patent professionals, including:
  - thread searching
  - keyword searching
  - IPC searching
  - sequence searching
- the advantages and limitations of search facilities on the Internet; and
- the advantages and limitations of commercial databases

For this exercise, please write down a search scenario that would be of value to you in your professional work or research. This could be an area of technology you work with, a researcher you are interested in, or a company you have been researching. For example, possible search scenarios could be:

- what is the most recent work on genetically engineered insulin - and what work has been done on deriving insulin from natural sources such as plants or animals?
- is there any recent progress in research on vaccines for malaria?
- what companies are doing research work on processed rice products?
- what patents nominate Herbert Boyer as inventor?
- what patents are owned by Genetech Corporation?
- how many patents were issued to Merck in 1999-2000?

What is your search scenario for this patent database searching exercise?

What are your findings?

FOREIGN AFFAIRS AND TRADE

AusAID the Australian Government's overseas aid program

Module Five

Group exercise on patent validity: neem oil patent

Intellectual Property and Biotechnology
A Training Handbook

Contents: Module Five

5.1 Objectives for Module Five

By the end of this Module you should have practical experience in how to:

- apply the legal principles relating to the validity of biotechnology patents
- assess whether an invention in patentable or not patentable having regard to issues of
  - novelty
  - inventive step
  - industrial application
  - usefulness
  - exceptions to patentability such as “ordre public”
  - whether the claims are supported in the description
- read an examination report and consider how to oppose the grant of a patent and get it revoked

5.2 Running the group exercise

The purpose of this exercise is to provide you with an opportunity to apply, in a practical context, the legal principles relating to the validity of biotechnology patents. This exercise will give you an opportunity to learn from the expertise and experience of your fellow participants in dealing with a practical task.

If possible, you can do this exercise by dividing into four small groups. Each group would take a different role in working with a claimed invention and patent claims. Each group is allocated particular materials to assist in this role.

Please note that this exercise aims to make you familiar with some key skills needed to consider biotechnology patents and validity. This exercise will not make 'instant experts' out of everyone, but should help illustrate some of the processes and ways of analysing problems that people working with patents need to understand.

The four groups for this exercise have distinct roles in relation to a patent document, reflecting various ways in which patent documents are analysed:

Group A	takes the role of the patent agent or patent attorney preparing a patent specification
Group B	takes the role of a patent office examiner analyzing the patent application
Group C	takes the role of a party concerned about the patent
Group D	takes the role of another commercial enterprise concerned about the impact of the patent on its operations

Which law applies? There are significant differences in patent law between different countries, and so the same invention could well be judged in different ways depending on the law that applies. For example, the same invention could be accepted under one patent law as patentable, and rejected under another patent law on the grounds that it is not acceptable subject matter or that it lacks an inventive step, even though both the laws in question comply with the same international standard of the TRIPS Agreement.

This exercise can be considered under any patent law. It is based on a European patent case (in other words, on a regional patent application filed with the European Patent Office in Munich), so you may like to consider it under the relevant European patent law (contained in the European Patent Convention). Alternatively, you might like to consider the case under another patent law you have available – for instance, the patent law of your own country.

If possible, you could consider the case under two different laws – your own country's patent law, and the European law. In practice, people working with patents often have to consider the different scope of patent law in the various countries where they would like to gain protection. It is often necessary to draw up different patent claims to comply with these differences in patent law.

5.3 Background to Neem

The patents on Neem

The Neem patent (Hydrophobic extracted neem oil – a novel insecticide and fungicide) has been chosen because its claims are relatively simple and still capture some of the key concerns of patentability in the biotechnology field. This patent also highlights cross-jurisdictional issues discussed in the course of this workshop and highlights some of the issues that as biotechnology patent examiners, and agri-biotechnology researchers will have to contend with on a daily basis.

This particular patent has been particularly controversial, with particular opposition from India on the ground that the patent is not novel or lacks inventive step. The European Patent Office Division of Opposition has recently revoked the European version of the patent (0 436 257 Al), while different versions of the patent (generally with different claims) in other countries remain in force, demonstrating the topicality and relevance of this exercise.

The following scenario is generally based on the original case, although the facts and prior art referred to have been considerably limited in scope to make the exercise workable. This exercise does not attempt to replicate the legal situation of the original patent case, and should not be viewed as an authoritative legal analysis of this case. It is, rather, an exercise aimed at promoting discussion of the patent issues raised by this case.

The use of the neem tree has become highly controversial, with claims of biopiracy and appropriation of traditional knowledge being laid. This exercise does not go fully into these issues, but participants should be aware that, beyond the specific patent issues raised here, there are broader questions of ownership and exploitation of traditional knowledge and biological resources. After the specific patent exercise is completed, it may lay the basis for much broader discussion of these issues.

The Neem tree

The Neem tree has been used for a wide variety of practical purposes, both medicinal and agricultural. It is present in most countries in the Asia Pacific region, sometimes under different names (for instance, it is also known in Indonesia as Intaran, Mempheuh, Imba, Mindi and Mimbo; in English, it is also known as Margosa). It is well known as a source of traditional remedies – so much so that it is commonly known as the 'village pharmacy.' It has been seen in traditional cultures as a communal resource. Traditionally, juice extracted from the neem's leaves have been used to treat skin infections, and neem twigs have been used to clean teeth. Various neem extracts have been used as tonics, and in agriculture and food processing as a fungicide and insecticide. Neem is also involved in a number of traditional rituals – for instance, its leaves and branches are used in a ritual in order to bring rain. This exercise relates to the agricultural value of neem's fungicidal and insecticidal properties.

The botanical name of Neem is *Azadirachta indica A.Juss.* This is derived from the Persian name of the tree: *azad deracht*, or 'free tree.' Its origins lie in Asia, probably in the Indian subcontinent, but it is found in dry forest areas throughout South and Southeast Asia including Pakistan, Sri Lanka, Burma, Thailand, Malaysia and Indonesia, where its various beneficial properties have been traditionally known and used in differing ways.

The tree is very widespread, well beyond its origins in Asia, and has been cultivated in Africa, America, the Middle East and Australia. It grows in a variety of habitats up to an altitude of 1,500 metres. Neem grows to height of about 20 metres and a girth of 25 metres. It grows well on dry, stony, clay and saline soils and has a strong root system that extracts nutrients and moisture from poor soils.

Chemistry of the Neem tree

The chemistry of the neem tree is complex. It contains thousands of chemicals, among which are over a hundred terpenoids (a particular class of hydrocarbons found in volatile plant oils, such as turpentine, itself originally derived from a tree, the *Pistachia Terebinthus*). Some terpenoids are apparently unique to the neem tree and some other members of its family. These include the compound azadirachtin (a name derived from *azad deracht*, the Persian name of the neem). Salannid has also been studied. According to some studies, a strong concentration of azadirachtin is essential for a neem extract to have effect as a pesticide or fungicide.

For example, the website www.pioneerherbs.com indicates that: 'The active ingredient azadirachtin is found in commercial insect growth regulators. The key insecticidal ingredient found in the neem tree is azadiracthin…' It suggests that azadiractin blocks the insect's production of certain vital hormones, and also deters insects from eating.

Most traditional preparations derived from the neem make use of a more general mixture of these chemicals, and derive their effective properties from a range of chemicals. These terpenoids can be found in all parts of the plant, although they are most highly concentrated in the kernels of the seeds. The kernels contain about 30-40% oil, some 2.5-3.0% triterpenoids, and between 0.2 to 0.6% of azadirachtin.

Agronomy of the Neem tree

The neem tree is propagated by its seed, which can normally be used up to about three weeks after being harvested. It is also propagated by stem and root cuttings. The tree will begin to bear fruit within three to five years, and is fully productive after about a decade. It can live for up to two hundred years. The neem's leaves, stem, fruit and seed are all used in creating beneficial extracts, many of which have high concentrations of azadirachtin. According to some studies, neem honey and the latex pressed from the unripe fruits appears to be essentially free of azadirachtin. Much of the present case revolves around the perceived importance of azadirachtin.

The neem patent case study

This case study is based on an actual patenting case, namely European Patent 436257, filed in December 1990, which was the subject of a revocation challenge. For the sake of the exercise, we will assume that the research described in this patent is being done by an hypothetical research institute, the Better Nature Institute.

The exercise concerns research into extracts from the neem tree, with the aim of producing pesticides and fungicides suitable for a wide range of applications. Pesticides are used to repel or destroy insect pests in agriculture, while fungicides are used to kill damaging fungi such as moulds, rusts and mildew.

In the exercise, we assume that the Better Nature Institute is undertaking a research project, which is looking into how to derive useful extracts from the neem tree, in a selective way so that specific chemicals are excluded and specific chemicals are included. This research project is in fact based directly on one of the experiments described in the technical disclosure in the actual patent.

Extracting oils or essences from natural products normally involves either crushing or pressing the product, or using solvents to extract soluble chemicals from the product, or a combination of both techniques. Traditionally, neem oil has been prepared by mechanically pressing the neem seeds and recovering the oil that produced from the press, or by using conventional solvents to yield an extract.

Many solvents are well known and widely used, as part of common general knowledge in science and industry, including in traditional science and industry. Water is of course the most widely used solvent, and it dissolves many substances – these are known as 'hydrophilic' ('water-loving') chemicals. For other 'hydrophobic' (water resistant) chemicals, other solvents are available, generally organic chemicals – for example, benzene, alcohols (such as ethanol and methanol) or hydrocarbons such as hexane and pentane. The various properties and uses of these solvents are very well known and they are very widely used in industry and science. The chemical properties of water are partially due to the 'polar' structure of its molecule (it has positively and negatively charged ends) – it is this property that makes it react with many substances and dissolve them. The molecules of hydrophobic organic solvents, such as hexane, generally have a non-polar structure, which means that there are no distinct positively and negatively charged regions.

The most widely studied chemical that is present in the neem tree is azadirachtin, discussed above. Azadirachtin is recognized as being an important ingredient in neem oils used for insecticides and pesticides. For the sake of this exercise, it appears to be soluble in water, but it seems not to be soluble in non-polar hydrophobic solvents such as hexane.

There have been many publications on the pesticidal and fungicidal qualities of the neem tree and its various extracts. One publication on the use of neem to produce a pesticide is as follows (this is an edited version of a method published on www.neemfoundation.org, which is a valuable source of information on neem):

Neem Kernel extract: 50g of Neem kernel is required for use in 1 litre of water. The kernel is pounded gently, so that no oil comes out. … The seeds … should be at least 3 months old and should not be used after 8-10 months. Before 3 months or after 8 months, the azadirachtin quantity is quite low in the seed and hence it cannot efficiently be used for pest control.

The pounded Neem kernel powder is gathered in a muslin pouch and this is soaked overnight in the water. The pouch is squeezed and the extract is filtered. To the filtrate, an emulsifier like teepol, sandovit, soap oil or soap cake powder is added. Emulsifier is added to helps the extract to stick well to the leaf surface.

Other known applications include:

- Neem leaf extract (obtained by soaking neem leaves in water overnight)
- Neem oil (the oil obtained by pressing neem seeds)
- Extract from neem cake (the 'cake' is what remains after the seeds have been pressed; the cake is soaked in water to obtain the extract)

These applications involve the use of water as a solvent. You will note that the description emphasizes the need for a high level of azadirachtin in the seed to ensure that the product is effective in pest control.

Other research projects have already looked into the properties of neem extracts obtained using different solvents. Water-based extracts have been widely explored. But other researchers have also used pentane, hexane, ethanol and methanol – many of the standard organic solvents. The focus of the research already published appears to be concerned with two particular chemicals – azadirachtin and salannin. For the sake of this exercise, we assume that these chemicals appear to be soluble in water, but not in non-polar organic solvents.

The research team starts work. The first experiment went as follows:

1. 80 kg of dried neem seeds were milled to a certain size.

2. The ground seeds were added to a vessel together with 259 litres of hexane and agitated for 18 hours. A centrifuge was used to separate the extracted seeds from the hexane-neem oil solution.

3. The hexane-neem oil solution was heated to 75° C to remove the excess hexane. The neem oil then had less than 1% hexane and only 0.01% of azadirachtin.

4. The extracted neem oil was then mixed into water at 1% and 3% concentrations. A surfactant chemical was added.

5. 25 chrysanthemum plants were placed in a whitefly colony for 24 hours, removed, and sprayed with a water-mist to remove the adult whiteflies from the plants. This left behind eggs on the leaves of the plants.

6. The plants were divided into 5 groups of 5 and treated as follows:
   Group 1) sprayed with water 0 days after exposure to whiteflies (control group),
   Group 2) sprayed with 1% neem oil formulation 0 days after exposure to whiteflies,
   Group 3) sprayed with 3% neem oil formulation 0 days after exposure to whiteflies,
   Group 4) sprayed with 1% neem oil formulation 4 days after exposure to whiteflies, and
   Group 5) sprayed with 3% neem oil formulation 4 days after exposure to whiteflies.

   The two last groups were sprayed 4 days after exposure, because whitefly eggs usually hatch 5-6 days after they are laid on the leaf, and this would ensure the spray was still present when the eggs hatched.

The results were as follows:

Group	Treatment	Eggs	Dead Nymphs	Mortality rate (%)
1	Water only on day 0	317	2	0
2	1% neem oil on day 0	185	100	54
3	3% neem oil on day 0	153	143	93
4	1% neem oil on day 4	198	180	90
5	3% neem oil on day 4	360	358	99

The experiment demonstrated that the extracted neem oil was an effective insecticide at both concentrations and at both exposure times. It was observed that most nymphs died as they were emerging from the egg case. It was most effective at 3% concentration.

The Better Nature Institute believes that this experiment has produced an interesting, unexpected and potentially useful new outcome. It decides to file a patent application in Indonesia. In this Patent Law Exercise, four groups play different roles in relation to this patent.

GROUP 1:
PATENT AGENT FOR THE BETTER NATURE INSTITUTE

Your role

You are a patent agent or patent attorney, engaged by the Better Nature Institute to draw up a patent application for this invention in your country.

If you have it available, use the patent law of your own country and apply the specific tests it provides for. Alternatively, you could use the extracts from European Patent Law provided in this Module.

Your task

Based on the description of the experimental outcome and the known prior art in the above introduction to this exercise, prepare:

- a search strategy for determining relevant prior art
- a patent claim or claims for a patent application that meets the requirements of your country's patent law

Questions to consider:

- What kind of searching or research would you undertake before preparing the patent claim?
- What problem does the invention aim to solve?
- What is already known about this area of technology?
- What approaches do the prior art suggest?
- How does this invention uniquely solve the problem?
- What is unexpected about this outcome?
- Is the invention a new method, a new product, or both?
- How can the invention be defined in writing so as to meet the requirements of:
    - The basic definition of an invention?
    - Any exceptions to patentable material that may apply in the law (e.g. plant varieties, contrary to public order, etc.)?
    - Novelty?
    - Inventive step or non-obviousness?
    - Industrial application or utility?
    - Support by the technical disclosure of the experiment and its outcomes?
- How would you ensure that the main (independent) claims were broad enough to protect your client's interests, and to defeat attempts to take the essence of your client's invention?
- How could you narrow the scope of the invention in dependent claims, so as to provide levels of protection for the patent against attacks on its validity?

GROUP 2:
PATENT EXAMINER, PATENT OFFICE

Your role

You are a patent examiner, responsible for plant products and biotechnology inventions. You can choose to take the role of:

- an Examiner in the European Patent Office (EPO), in the Biotechnology section, or
- an Examiner in another national patent office.

This patent was originally considered in the EPO, but you may wish to examine it as though it were an application under your own national patent law.

If you choose to be the EPO Examiner, you will need to refer to the extracts from European patent law.

If you choose to be an Examiner in another patent office, you will need to have access to the patent law that applies in that country.

Your task

The exercise is based on the attached patent document (Document 1 - this is actually European patent application EP 0 436 257, but for the purpose of this training exercise we treat it as a patent application under the relevant national law in the name of the Better Nature Institute). You are required to examine it under patent law to see if it meets the required standards.

- If you decide to take the role of EPO Examiner, you should examine the Application to see if it complies with the provisions of the European Patent Convention (EPC) dealing with Patentability and Filing Requirements. The relevant extracts of Part II Chapter I and Part III Chapter I of the EPC are in Document 2. You are to determine the extent to which the Application satisfies these requirements.
- If you choose a different national law, then you should first identify what that law says on:
    - definition of an invention
    - any excluded categories of invention (such as contrary to morality)
    - novelty, including the definition of relevant prior art or prior publication
    - inventive step, or non-obviousness, including any definition of common general
    - utility or usefulness
    - unity of invention, or the need for the claims to cover one single inventive concept, and
    - the need for the claims to be fully supported by, or fairly based, on the disclosure in the patent document.

The application

The patent application gives details of the research project already described above. It also describes further experiments into the use of this particular neem oil as a pesticide and fungicide. The Application concerns a fungicide and insecticide comprising neem oil substantially free of azadirachtin and salannin.

The main claims, respectively concerning a product and a method, are:

1. An insecticide and foliar fungicide comprising neem oil which is substantially free of azadarachtin and salannin, said neem oil prepared by:
   a. extracting dried, coarsely ground neem seeds with a non-polar, hydrophobic solvent to obtain a neem oil extract
   b. removing the solvent to obtain the neem oil product

10. Use of the insecticide and foliar fungicide according to claims 1 to 5 for controlling insect pests and fungi comprising contacting the insect or fungi with a neem oil formulation containing 0.1% to 10% neem oil which is substantially free of azadirachtin or salannin, 0.005% to 5% emulsifying surf actant and 0 to 99% water.

Questions to consider:

Review the prior art already described in the introduction to this exercise

Consider both the insecticide/fungicide product (claim 1), and the claimed used of the product (claim 10).

Is it an invention? Does it fit within the general definition of an invention? Do any exceptions on patentability apply? Are these claims directed to the same invention, or to two separate inventions?

Is it novel:

- in its absence of azadarachtin and salannin?
- in being produced by the defined solvent?

Is the choice of the solvent together with the absence of these chemicals sufficient for novelty?

This question requires a comparison between each claim of the Application and what is disclosed in the state of the art. A claim will not be novel if it relates to subject matter which is disclosed in the state of the art. Does any of the information provided reveal part of the state of the art? Is the subject matter of any claim disclosed in the state of the art?

Does it have an inventive step in accordance with the requirements for inventiveness or non-obviousness:

- In the choice of extraction technique?
- In the surprising quality of the results?
- In the light of the known use of different solvents?

This question requires a consideration of whether the subject matter of each claim is obvious to a person 'skilled in the art'. What type of person is skilled in this art? What would be obvious to that type of person?

What is the common general knowledge in this field? Consider the prior art you have been given as evidence of common general knowledge. What other sources of information could be used as background to the question of what is obvious to the person skilled in the art?

Is the claimed invention industrially applicable or useful?

Is the subject matter of each claim capable of being made or used in any kind of industry? What is an "industry"? Is there an industry in which the subject matter of each claim can be made or used?

- Does the invention fit any of the specific exceptions to patentable inventions in the law you are applying?
    - Is it a discovery? For example, if you are referring to the European patenting requirements, are any of the claims excluded by article 52(2)(a) of the European Patent Convention? That is, are any of the claims discoveries? This question requires a consideration of what is a "discovery" and also of what is the meant by the "as such" qualification imposed by article 52(3). Is the H2 gene naturally occurring? If so, does that make the claims to it a discovery as such? Does disclosing the DNA and amino acid sequences make the claims to subject matter more than a discovery as such?
- Are any of the claims excluded by article 52(4) of the European Patent Convention? That is, are any of the claims for methods for treatment of the human body by surgery or therapy? This question requires a consideration of what is a method for the treatment of the human body by surgery or therapy. Does this include subject matter that may be used or involved in such a treatment?
- Are any of the claims excluded by article 53(a) of the European Patent Convention? That is, are any of the claims contrary to "ordre public" or morality? This question requires a consideration of what is meant by "ordre public" and what is "contrary to law". How is the relevant public policy/policies to be identified? Are there policies in favour of granting the patent? What law(s) might the invention conflict with?

Does the invention meet other requirements, such as clarity and support from the disclosure?

- For example, do the claims satisfy article 84 of the European Patent Convention? That is, are the claims clear and concise and supported by the description? This question requires an analysis of whether there is any ambiguity or lack of definition of subject matter in each claim. What is the subject matter of each claim? Has it been adequately defined?

GROUP 3:
ASIAN ALLIANCE AGAINST BIOTECHNOLOGY MONOPOLIES

Your role

You are a campaign team for the Asian Alliance against Biotechnology Monopolies, a non-governmental organization concerned with biotechnology issues.

Your task

You are concerned that the attached patent (based on European patent EP 0 436 257, treated as a hypothetical for the sake of this exercise) unfairly restricts the availability and use of neem tree oil, and that the patent owner could unreasonably benefit from traditional knowledge about the properties of neem. You are planning to apply to have the patent revoked under patent law. Your task is to prepare a draft lawsuit to support your claim.

The attached patent is a European patent, and so can only be challenged in the European Patent Office. For the sake of this exercise, you can choose either to challenge the patent under the EPO system, or you can assume that the patent is actually a national patent in another jurisdiction (for instance, your own country), and challenge it under the national patent law of that jurisdiction. For example, for the sake of this exercise, you could assume that this patent was actually an Indonesian patent, and consider how it could be challenged under Indonesia's current patent law.

- Analyse the grounds for invalidity or opposition to a patent in the law you are using. If you decide to take the role of EPO Examiner, you should consider the provisions of the European Patent Convention (EPC)
- If you choose a different national law, then you should first identify what that law says on the grounds for opposition or revocation, for instance in relation to:
    - definition of an invention
    - any excluded categories of invention (such as contrary to morality)
    - novelty, including the definition of relevant prior art or prior publication
    - inventive step, or non-obviousness, including any definition of common general
    - utility or usefulness
    - unity of invention, or the need for the claims to cover one single inventive concept, and
    - the need for the claims to be fully supported by, or fairly based, on the disclosure in the patent document.

The patent

The patent gives details of the research project already described above. It also gives further evidence of the use of this particular neem oil as a pesticide and fungicide.

The main claims are:

1. An insecticide and foliar fungicide comprising neem oil which is substantially free of azadarachtin and salannin, said neem oil prepared by:

    a. extracting dried, coarsely ground neem seeds with a non-polar, hydrophobic solvent to obtain a neem oil extract

    b. removing the solvent to obtain the neem oil product

10. Use of the insecticide and foliar fungicide according to claims 1 to 5 for controlling insect pests and fungi comprising contacting the insect or fungi with a neem oil formulation containing 0.1% to 10% neem oil which is substantially free of azadirachtin or salannin, 0.005% to 5% emulsifying surfactant and 0 to 99% water.

Questions to consider:

Address your objections to both the insecticide/fungicide product (claim 1), and the claimed used of the product (claim 10):

How can you argue that the invention is not novel?

- In relation to the absence of azadarachtin and salannin?
- In being produced by the defined solvent?

How can you argue that the invention lacks an inventive step?

- In the choice of extraction technique?
- In the light of the nature of the results of this technique?
- In the light of the known use of different solvents?

How can you argue that the claimed invention is not industrially applicable?

Does the invention fit any of the exceptions to patentable inventions? For instance, can you argue that it is contrary to regulations, public order or morality?

What other objections to the patent can you think of?

GROUP 4:
PATENT CONSULTANT FOR PT BIOENTERPRISE, AN INDONESIAN COMPANY

Your role

You are a Patent Consultant, engaged by PT Bioenterprise, an Indonesian company specializing in producing products based on natural products.

Your task

PT Bioenterprise is working on a new product, based on traditional use of neem products. It is a spray to be applied to the skin, which repels mosquitoes. This is obtained by crushing neem seeds in a mill, mixing them with an alcohol distilled by a traditional technique from fermented neem tree twigs and leaves, and warming the mixture to reduce and thicken it. This method drew on a traditional technique that your client believes was used in Sumatera Barat (West Sumatra), although the details aren't clear. Your client is still undertaking research, but proposes to develop a new product, manufacture it in Indonesia, and export it throughout the East Asian region, where mosquitoes are a major nuisance and health problem.

You have done a patent search for your client and found the attached patent document, issued in Indonesia in the name of the Better Nature Institute (this is actually European patent EP 0 436 257, but in this exercise we treat it as an application under Indonesian law).

You are concerned that this patent could interfere with your client's business activities, and after a conference with the company, you are asked to draw up a legal opinion on whether the patent could be a problem and how that problem could be addressed.

In assessing this case, use the patent law of any country – for instance, use the patent law that applies in your own country.

The patent

The patent gives details of the research project already described in the introduction. It also gives further evidence of the use of this particular neem oil as a pesticide and fungicide.

The main claims are:

> 1. An insecticide and foliar fungicide comprising neem oil which is substantially free of azadarachtin and salannin, said neem oil prepared by:
>
> (a) extracting dried, coarsely ground neem seeds with a non-polar, hydrophobic solvent to obtain a neem oil ex tract
>
> (b) removing the solvent to obtain the neem oil product
>
> 10. Use of the insecticide and foliar fungicide according to claims 1 to 5 for controlling insect pests and fungi comprising contacting the insect or fungi with a neem oil formulation containing 0.1% to 10% neem oil which is substantially free of azadirachtin or salannin, 0.005% to 5% emulsifying surfactant and 0 to 99% water.

Questions to consider:

Does your client's product amount to an infringement of these claims? Can your client continue its research and development program? At what stage of product development would it

What do you need to find out about your client's product and the process for making it? What are the legal and the technical issues? What sort of information would be useful in

safeguarding your client's interests – for example, what sort of information would prove that the patent was not novel or was obvious?

What elements of the claims are relevant to your client's interests?

What are the options under the Patents Law to safeguard your client's interests – for instance, provisions concerning opposition, reexamination, compulsory licensing or patent revocation/cancellation?

What information and evidence do you need to strengthen your client's position?

5.4 Attachments

Document 1: **European Patent Application No. 90250319.2**

Document 2: **European Patent Convention 1973 – Part II Chapter I, Part III Chapter I, Part V and Part VI (selected provisions)**

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 436 257 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **90250319.2**

(51) Int. Cl.5: **A01N 65/00**

(22) Date of filing: **20.12.90**

(30) Priority: **26.12.89 US 456762**

(43) Date of publication of application:
10.07.91 Bulletin 91/28

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(71) Applicant: **W.R. Grace & Co.-Conn.**
Grace Plaza, 1114 Ave. of the Americas
New York New York 10036(US)

Applicant: **THE UNITED STATES OF AMERICA as represented by THE SECRETARY OF AGRICULTURE**
United States Department of Agriculture
Washington, DC 20250(US)

(72) Inventor: **Locke, James Charles**
3473 Bruton Parish Way
Silver Spring, Md. 20904(US)
Inventor: **Larew, Hiram Gordon III**
3312 Gumwood Drive
Hyattsville, Md. 20783(US)
Inventor: **Walter, James Frederic**
1008 Ashland Drive
Ashton, Md. 20861(US)

(74) Representative: **UEXKÜLL & STOLBERG**
Patentanwälte
Beselerstrasse 4
W-2000 Hamburg 52(DE)

(54) Hydrophobic extracted neem oil - a novel insecticide and fungicide.

(57) A novel insecticide and foliar fungicide derived from a neem seed extract comprising neem oil which is substantially free of azadirachtin and salannin, said neem oil being prepared by extracting dried, coarsely ground neem seeds with a non-polar, hydrophobic solvent to obtain a neem oil extract, and then removing the solvent to obtain the neem oil. These neem oil pesticides exhibit the ability to repel insects from plant surfaces, prevent fungal growth, and kill insect and fungal pests at various life stages.

EP 0 436 257 A1

HYDROPHOBIC EXTRACTED NEEM OIL - A NOVEL INSECTICIDE AND FUNGICIDE

Background of the Invention

Field of the Invention

This invention relates to novel pesticide compositions derived from neem seeds, and more specifically to a novel insecticide and foliar fungicide comprising a hydrophobic-solvent extracted neem oil. These neem oil pesticides exhibit the ability to repel insects from plant surfaces, prevent fungal growth and kill insect and fungal pests at various life stages.

Description of Prior Art

The neem tree, a tropical evergreen, has been used for centuries as a source of pesticides to which insects have not developed a resistance. Various neem seed extracts, particularly the ones containing the hydrophilic, tetranortriterpenoid azadirachtin, are known to influence the feeding behavior, metamorphosis (insect growth regulating [IGR] effect), fecundity, and fitness of numerous insect species belonging to various orders.

It is known that neem oil, containing azadirachtin, may be mechanically pressed from neem seeds in the cold by using oil presses or may be extracted using alcohols or other solvents using Soxhlet apparatus. Small amounts of neem oil can be obtained by kneading neem seed powder by hand after adding some water (Schmutterer & Helip 1988). Thus the term 'neem oil' has been used to describe a variety of materials containing a mixture of both hydrophilic and hydrophobic extractables. The variety of extraction methods and resultant variety in composition of neem oil has led to great confusion as to the true properties of "neem oil". Khan and Wassilew (1986) tested the effect of their "neem oil" (prepared by aqueous extraction of neem kernels) on 14 common fungi, including Trichophytonrubrum, T. violaceus, T. concentrichus, T. mentagrophytes, Epidermophyton floccosum, Mierosporum citaneum, Scrophulariopsis brevicaulis, Geotrichum candidum and Fusarium sp and found that it did not inhibit fungal growth and, in fact, the neem oil itself actually contained several species of growing fungi. Yet an anonymous article (Anon 1986) reported that "10% Neem oil diluted from its emulsifiable concentrate formulation" completely inhibited several species of fungi such as Aspergillus niger, Fusarium moniliforme, Macrophomina phaseolina and Drechslera rostrata. However, the specific details of this formulation were not provided.

Similarly, there are discrepencies in the literature as to the use of neem oil to control insects. Schmutterer and Hellpap (1986) showed that aqueous neem seed extracts are significantly superior to neem oil in repelling leaf mites (Scrobipalpa ergasina), leaf roller (Phycita melogenu) and leaf hopper (Jacobiella facialna). While Mansour et al. (1986) report that the pentane extract of neem seeds was much more effective at controlling the spider mite Tetranychus cinnabarinus than were ethanol or methanol extracts, but surprisingly, the pentane extract was less effective at controlling the mite, Phytoseiulus persimilis than were the ethanol or methanol extracts.

Yamasaki, et al showed that the tetranortriterpenoid, salannin, can be isolated from crude plant extracts, obtained from Indian neem seeds which are known to be high in salannin content, using hexane. The biological activity of the salannin extract is reported to be feeding deterency and growth inhibition when applied to chewing insects such as beetles and caterpillers.

This invention clarifies the discrepancies in the prior art and provides a novel neem oil extract that is substantially free of azadirachtin and salannin and yet is effective as both a foliar fungicide and an insecticide.

It has now been discovered that under the process of this invention, a non-polar hydrophobic-solvent extracted neem oil, substantially free of azadirachtin and salannin, possesses the ability to repel insects from plant surfaces, kill insects at various life stages in particular the egg and larval stages, and control the growth of serious fungal pathogens. This dual activity as both an insecticide and fungicide in the absence of azadirachtin is novel and unique.

The insecticide and fungicidal activities of hydrophobicly extracted neem oil is unique and unexpected in view of the absence of any known active ingredients.

Summary of the Invention

It is an object of this invention to provide a novel pesticide that repels insect pests from plant surfaces

and kills insects at various life stages in particular the egg and larval stages, and controls the growth of various fungi.

Another object of this invention is to provide a natural pesticide formulation derived from neem seed extracts for the protection of plants from various insect or fungal pests.

In accordance with the present invention, there have been provided certain novel pesticide formulations derived from neem seed extracts, said formulations comprising non-polar hydrophobic-solvent extracted neem oil fractions, that are substantially free of azadirachtin and salannin.

Detailed Description

Some active ingredients of the seeds and leaves of the tropical neem tree, Azadirachtin indica, particularly the tetranortriterpenoids azadirachtin and salannin, are known for their potent pesticidal activities. The present invention is directed to various pesticide formulations prepared from neem oil which are substantially free of azadirachtin and salannin, and yet said formulations possess the ability to repel insect pests from plant surfaces, kill insect pests at various life stages in particular the egg and larval stage, and control fungal pathogens.

Neem seeds can be quite variable in size, shape and composition. Seeds from around the world can be as small and round as a pea and as large and long as a bean. Neem seeds consist of two parts, a shell that does not contain oil or pesticidal activity and the kernal which contains oil and azadirachtin. However, the composition of seeds collected from throughout the world varies considerably as shown in Table A. In particular we have found that oil derived from neem trees with high azadirachtin concentration is both insecticidal and fungicidal.

Table A

Seeds Source	% Kernal in Seed	% Volatile	Content Oil %	AZAD mg/gsk*
Senegal (Pout)	54	7	22	6.6
India (Punjab)	55	5.8	30	1.6
Togo (Atkpame)	57	7.3	27	4.5
Haiti (Arcahie)	51	12.0	19	2.7
Ghana (Bawk)	57	6.4	14	3.9

*gsk = gram seed kernel

The pesticide formulations of this invention are prepared from neem oil which has been extracted from, dried, coarsely ground neem seeds with a suitable non-polar, hydrophobic solvent. In accordance with this invention, dried neem seeds, typically containing about 5 to 15% water, are coarsely ground to about 5 mesh. The ground neem seeds are then extracted with a non-polar hydrophobic solvent to remove neem oil. It is preferred to use a significant excess of solvent (3 to 1 w/w) to obtain good yields. The solvent must be suitably hydrophobic to prevent excess water from contaminating the product. Water in the extract will cause azadirachtin to be extracted from the seeds and result in hydrolysis of the extract. After extraction, the solvent is removed from the extract by low temperature evaporation, preferably by vacuum evaporation to yield the neem oil product.

Final pesticide formulations, in accordance with this invention, can be prepared by diluting the neem oil with about 5 to 50% preferably 5 to 20% and most preferably 7 to 15% by volume emulsifying surfactant and may optionally contain 0-1% PABA. Suitable emulsifying surfactants include sorbitan esters, ethoxylated and propoxylated mono and diglycerides, acetylated mono- or diglycerides, lactylated mono- or diglycerides, citric acid esters of mono- or diglycerides, sugar esters, polysorbates, poly-glycerol esters, and the like, and mixtures thereof. The preferred emulsifying surfactants are the polyoxyethylene derivatives of fatty acid partial esters of sorbital anhydrides which are sold under the name Tween 20, Tween 40, Tween 60 and Tween 80. Prior to final application, these pesticide formulations are typically diluted with water.

For foliar application it has been observed that rates of 0.1 to 10%, preferably 0.25 to 3% neem oil diluted in water is effective for control of insect pests and fungal diseases without unacceptable plant

damage. Neem oil may also be used at various dilutions to control various pest and disease problems on turf, horticultural and agricultural crops as well as stored fruits and vegetables. The neem oil formulations have been shown to be effective at controlling such pests as Colorado Potato Beetle, Diamond Backed Moth, Whitefly, Mealy bug, Aphids, Hornworm, Lacebug, mites, fleas, ticks, mosquitoes and flies and the like. They are also effective at controlling fungi such as mildews, rusts, dollar spot, brown patch, black spots, botrytis, and the like. Furthermore, the neem oil can be used to control parasitic pests on mammals such as lice, ticks, scabies, as well as eczema and dermatitus.

Suitable non-polar, hydrophobic solvents for use in extracting the neem oil from the ground neem seeds will include those solvents having high neem oil solubility and substantially no azadirachtin or water solubility. The preferred non-polar solvents include, but are not limited to, aliphatic hydrocarbons and halogenated aliphatic hydrocarbons such as pentane, hexane, heptane, octane, nonane, decane, isooctane, chloropentane, chlorohexane, and the like, and their isomers; petroleum distillates, petroleum ether, and the like; aromatics and substituted aromatics such as benzene, toluene, chlorobenzene, benzaldehyde, xylenes, and the like; and mixtures thereof. Various other non-polar solvents having the above characteristics are well known to those skilled in the art, and the choice of a particular solvent is not per se critical to the invention, provided that it is substantially azadirachtin-insoluble and neem oil has a high degree of solubility therein.

Without further elaboration, it is believed that one skilled in the art, using the preceding detailed description can utilize the present invention to its fullest extent. The principles, preferred embodiments and modes of operation of the present invention have been described in the foregoing specification. The following examples are provided to illustrate the invention in accordance with the principles of this invention, but are not to be construed as limiting the invention in any way except as indicated in the appended claims. Variations and changes may be made by those skilled in the art without departing from the spirit of the invention. All parts and percentages are by weight unless otherwise indicated.

Example 1

This example illustrates the effectiveness of the non-polar, hydrophobic-solvent extracted neem oil formulations of this invention on newly laid or near-to-hatch greenhouse whitefly (Trialeurodes vaporariorum) eggs. Eighty (80) kgs of dried defruited neem seeds from Africa were ground in a cutting mill to about 10 mesh. The ground seeds were added to a 300 gallon agitated vessel together with 140 gallons (259 kgs) of hexane and agitated for 18 hours. The extracted seeds were then separated from the hexane-neem oil solution by centrifugation. The hexane-neem oil solution was transferred to a 500 ml jacketed agitated vessel where the solution was heated to 165° F to remove the excess hexane. The recovered neem oil had a hexane content of 1%. The extracted neem oil was formulated into respective 1% and 3% solutions in 100 mls of water containing 1 drop of surfactant (Ivory™ Liquid). To test the effectiveness of these formulations, 25 potted chrysanthemum plants, cv. Iceberg, had all but 3 fully-expanded leaves removed. The plants were placed in a whitefly colony for 24 hours, removed, and sprayed with a water-mist to remove the adult whiteflies from the plants. The plants were divided into 5 groups of 5 and treated as follows:

Group 1) sprayed with water 0 days after exposure (DAE) to whiteflies,
Group 2) sprayed with 1% neem oil formulation 0 days after exposure to whiteflies,
Group 3) sprayed with 3% neem oil formulation 0 days after exposure to whiteflies,
Group 4) sprayed with 1% neem oil formulation 4 days after exposure to whiteflies, and
Group 5) sprayed with 3% neem oil formulation 4 days after exposure to whiteflies.

The greenhouse whitefly eggs usually hatched 5-6 days after oviposition, thus the 4 DAE treatments were applied near the time of egg hatch. Once all the eggs had hatched on the control plants (those sprayed with water), the effectiveness of the oil fraction was assessed by counting the unhatched eggs and dead nymphs per leaf. The results were as follows:

Table 1

Effect of Neem Oil When Sprayed on New and 4-Day-Old Greenhouse Whitefly Eggs Laid on Chrysanthemums

Treatment	Eggs*	Dead Nymphs*	% Mortality**
Water	317ab	2c	0
1%, 0 DAE	185b	100bc	54
3%, 0 DAE	153b	143b	93
1%, 4 DAE	198ab	180b	90
3%, 4 DAE	360a	358a	99

* Values are means per 100 cm^2 leaf area. Means within trial followed by the same letter are not significantly different; DMRT, P = 0.05, N = 15 leaves.

** Number of dead nymphs divided by the number of eggs.

The extracted neem oil at both concentrations and exposure times caused significant nymphal mortality. It was observed that most nymphs died as they were emerging from the egg case. The extracted neem oil was most effective on the older eggs applied at a concentration of 3%.

Example 2

This example illustrates the effectiveness of extracted neem oil as a repellant to adult Bemisia tabaci whiteflies when sprayed on chrysanthemum foliage. The extracted neem oil was prepared and diluted into 1% and 3% formulation according to Example 1. To test the effectiveness of these formulations, nine 3-week-old potted chrysanthemum plants cv. Iceberg, having all but 3 fully expanded leaves removed, were divided into three groups of 3 and treated as follows:

Group 1) sprayed with water,
Group 2) sprayed with 1% neem oil formulation,
Group 3) sprayed with 3% neem oil formulation,

and then exposed to a colony of whiteflies for 24 hours. After exposure, the plants were cleaned of adult whiteflies and the number of eggs per leaf was determined. The results were as follows:

Table 2

Repellency of Neem Oils Against *Bemisia tabaci* on Chrysanthemums	
Treatment	Eggs*
Water	110.0a
1%	18.0b
3%	0.0b

* Values are means calculated per 100 cm² leaf area. Means followed by the same letter are not significantly different; DMRT, P = 0.05, N = 9 leaves.

The results show that extracted neem oil is effective at repelling Bemisia whiteflies at both concentrations.

Example 3

This example illustrates the longevity of repellant action of hydrophobic-solvent extracted neem oil when sprayed on chrysanthemum foliage cv. Iceberg. Repellancy was quantified by counting the number of greenhouse whitefly (Trialeurodes vaporariorum) eggs laid on leaves. Neem oil formulations were prepared according to Example 1. Forty eight 3-4 week old chrysanthemum plants cv. Iceberg having all but 3 fully expanded leaves removed, were divided into three groups of 16 plants each and treated as follows:

Group 1) sprayed with water,
Group 2) sprayed with 1% neem oil formulation,
Group 3) sprayed with 3% neem oil formulation.

On the same day as spraying (Day 0) 4 plants from each group were placed in a whitefly colony for 24 hours. On days 3, 7 and 14, 4 more plants from each group were exposed to the whitefly colony for 24 hours. After each exposure, the number of eggs per 100 cm^2 of leaf area on the top 2 treated leaves were counted. The results were as follows:

Table 3

Neem Oils -- Residual Effects				
Treatment	Mean No. Eggs/100 cm² Leaf Area*			
	Day 0	Day 3	Day 7	Day 14
Water	506a	844a	405a	72a
1%	69b	107b	14b	39ab
3%	18c	17b	1b	5b

*Means in same column followed by the same letter are not significantly different; DMRT, P=0.05, N=8 leaves.

The extracted neem oil formulations repelled ovipositing T. vaporariorum for up to 14 days after spraying. There were no clear differences in the level of repellancy between the 1% and 3% concentration, or the time between treatment and exposure.

Example 4

Control of Bean Rust by Extracted Neem Oil

Neem oil was extracted according to the procedure in Example 1. The extracted neem oil was mixed with water and diluted to 0.25, 0.5, and 1% and sprayed on the fully expanded primary leaves of beans cv. Pinto 111 until run off. The leaves were then inoculated with bean rust (Uromyces phaseoli) spores and placed in a dew chamber to allow infection. After approximately 16 hours the bean plants were removed from the dew chamber and placed in a greenhouse. After seven (7) days the number of rust pustules were counted. The results, in Table 4, show that the extracted neem oil is an effective foliar fungicide at these concentrations.

Table 4

Treatment	Pustules/100 cm^2*	% Control
Control	1174.4 a	0
0.25%	220.0 b	81.1
0.50%	116.6 b	90.2
1.00%	114.2 b	90.2

* Treatments with same letter are statistically similar; DMRT, P=0.05, N=6 leaves.

Example 5

Effect of Extracted Neem Oil and Margosan-O on the Repellancy of Whiteflies

Extracted neem oil as prepared in Example 1 was compared to Margosan-O a pesticide that contains the insect repellent azadirachtin. In these experiments 3 plants each were sprayed with water (control sample), a 2% solution of Margosan-O or a 2% solution of neem oil until run off. The plants were then placed in a chamber containing a colony of greenhouse whiteflies (Trialeurodes) for 2 hours. The plants were then removed from the chamber, the adults removed, and the number of eggs laid per cm^2 of leaf area counted. The results presented in Table 5 show that extracted neem oil is a much better repellent than Margosan-O for reducing egg laying by a factor of 6 compared to (Margosan-O the repellent) and by 45x over the control.

Table 5

Treatment	Eggs laid/cm^2 Area*	Repellent Factor
Control	8.70 a	0
Margosan-O	1.13 b	7.7
Extracted Neem Oil	0.058 c	150

Example 6

Control of Mildew on Hydrangea

A solution of 2% extracted neem oil in water was sprayed on 5 hydrangias plants growing in greenhouse. The treated plants and an equal number of untreated plants were exposed to the natural

mildew microrganisms found in the greenhouse for 6 weeks. At the end of this period the leaves of the plants were examined for mildew infestion. The untreated plants had an average of 46% of their leaves infested while the treated plants had 1.7% infestation.

Example 7

This example illustrates the potent ovicidal activity and repellent feeding deterrency of hydrophobic solvent extracts of neem seeds. Neem oil was extracted according to the procedure in example 1, and diluted with water and surfactant into 0.22%, 0.66% and 2.0% neem oil formulation. A series of tests were run on 6 types of insect eggs, both young and old including: Colorado potato beetle, tomato hornworm, housefly, Hawthorn lacebug, two-spotted spider mite, and greenhouse whitefly. The eggs were sprayed with water (as a control) and the 3 above neem oil formulations, and the number of hatching eggs was determined. The results were as follows:

Table VII

Ovicidal Activity of Neem Oil

Insect	Dose (%)	% Egg Mortality	
		Young Eggs	Old Eggs
Colorado Potato Beetle	0	8	13
	0.22	81	9
Tomato Hornworm	0	8	16
	0.22	11	26
	0.66	46	42
	2	90	77
Hawthorn Lacebug	0	26	33
	0.22	30	39
	0.66	32	41
	2	75	69
Two-Spotted Mite	0	16	12
	0.22	54	33
	0.66	81	52
	2	90	95
Greenhouse Whitefly	0	6	12
	0.22	20*	27*
	0.66	30*	42*
	2	41*	49*

*All treated insects died after hatching.

As is clear from the above table, the 2% neem oil was effective at controlling hornworm, lacebugs, mites and whitefly eggs whether they were young or old. Young Colorado potato beetle eggs were effectively killed by 2% neem oil.

Claims

1. An insecticide and foliar fungicide comprising neem oil which is substantially free of azadirachtin and salannin, said neem oil prepared by:
   a) extracting dried, coarsely ground neem seeds with a non-polar, hydrophobic solvent to obtain a neem oil extract,
   b) removing the solvent to obtain the neem oil product.

2. An insecticide and foliar fungicide according to Claim 1 wherein the non-polar, hydrophobic solvent is selected from the group of pentane, hexane, heptane, octane, isooctane, decane, nonane, petroleum distillates, petroleum ether, cyclohexane, chlorobenzene, benzaldehyde, benzene, toluene, xylene, and mixtures thereof.

3. An insecticide and foliar fungicide according to Claims 1 or 2 wherein the neem oil product is diluted with 5 to 50% by volume of an emulsifying surfactant.

4. An insecticide and foliar fungicide according to Claim 3 wherein the neem oil product is diluted with 5 to 20% by volume of an emulsifying reactant.

5. An insecticide and foliar fungicide according to Claim 3 wherein the neem oil product is diluted with 7 to 15% by volume of an emulsifying surfactant.

6. An insect ovicide comprising neem oil prepared according to Claims 1 to 5.

7. An insecticide having larvidical activity and insect repellancy comprising neem oil prepared according to Claims 1 to 5.

8. A fungicide for use on turf, horticultural and agricultural crops comprising neem oil prepared according to Claims 1 to 5.

9. An oviposition deterrent and repellant comprising neem oil according to Claims 1 to 5.

10. Use of the insecticide and foliar fungicide according to Claims 1 to 5 for controlling insect pests and fungi comprising contacting the insect or fungi with a neem oil formulation containing 0.1 to 10% neem oil which is substantially free of azadirachtin and salannin, 0.005 to 5% emulsifying surfactant and 0 to 99% water.

11. Use according to Claim 10 wherein the neem oil formulation contains 0.25 to 3% neem oil.

12. Use according to Claims 10 or 11 wherein the insect pests are selected from the group consisting of Colorado Potato beetle, Diamond Backed Moth, Whiteflies, leafminers, aphids, mealybug, hornworm, lacebug, mites, fleas, ticks, mosquitos, and flies.

13. Use according to Claim 10 wherein the fungi are selected from the group consisting of mildews, rusts, leaf spots, dollar spots, brown patch and botrytis.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 90 25 0319

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	ENTOMOLOGIA EXPERIMENTALIS ET APPLICATA, vol. 24, no. 3, 1978, pages 448-457; M. JACOBSON et al.: "Chemistry and biological activity of insect feeding deterrents from certain weed and crop plants" * Page 451, line 35 - page 453, line 39; page 455, line 22 - page 456, line 6 *	1-7,9-12	A 01 N 65/00
X	PHYTOPARASITICA, vol. 11, no. 3/4, 1983, pages 177-185; F.A. MANSOUR et al.: "Effects of neem (Azadirachta indica) seed kernel extracts from different solvents on the carmine spider mite, Tetranychus cinnabarinus" * Pages 179-184 *	1-7,9	
P,X	DE-A-3 912 059 (W. BOBLES) * Whole document *	1-7,9	
X	PHYTOPARASITICA, vol. 15, no. 2, 1987, pages 125-130; F. MANSOUR et al.: "Effects of neem (Azadirachta indica) seed kernel extracts from different solvents on the predacious mite Phytoseiulus persimilis and the phytophagous mite Tetranychus cinnabarinus" * Tables 1,2; page 129 *	1-5,7,9	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
X	PHYTOPARASITICA, vol. 14, no. 1, 1986, pages 73-76; F.A. MANSOUR et al.: "Toxicity of neem (Azadirachta indica) seed kernel extracts prepared with different solvents, on the spider Chiracanthium mildei" * Page 74, column 2, line 28 - page 75, column 1, line 5 *	1-5,7	A 01 N
X	CHEMICAL ABSTRACTS, vol. 103, no. 23, 9th December 1985, page 242, abstract no. 19142r, Columbus, Ohio, US; F.A. MANSOUR et al.: "Effects of neem (Azadirachta indica) seed kernel extracts from different solvents on the carmine spider mite, Tetranychus cinnabarinus", & SCHRIFTENR. GTZ 1984, 161(NAT. PESTIC. NEEM TREE OTHER TOP. PLANTS), 461-9 * Abstract *	1-5,7,9	

-/-

The present search report has been drawn up for all claims

Place of search	Date of completion of search	Examiner
The Hague	11 April 91	DONOVAN T.M.

CATEGORY OF CITED DOCUMENTS

- X: particularly relevant if taken alone
- Y: particularly relevant if combined with another document of the same catagory
- A: technological background
- O: non-written disclosure
- P: intermediate document
- T: theory or principle underlying the invention
- E: earlier patent document, but published on, or after the filing date
- D: document cited in the application
- L: document cited for other reasons

&: member of the same patent family, corresponding document

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 90 25 0319

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	JOURNAL OF ECONOMIC ENTOMOLOGY, vol. 71, no. 5, October 1978, pages 810-813; T.L. LADD, Jr. et al.: "Japanese beetles: Extracts from neem tree seeds as feeding deterrents" * Whole document *	1-5,10,11	
A	CHEMICAL ABSTRACTS, vol. 94, no. 5, 2nd February 1981, page 158, abstract no. 26058r, Columbus, Ohio, US; S. LAL et al.: "Use of pesticides and natural products in control of Sclerospora sacchari in maize", & TROP. PEST MANAGE. 1980, 26(3), 286-92 * Abstract *	1-5,8,10, 11,13	
A	BIOLOGICAL ABSTRACTS, vol. 71, no. 12, 1987, abstract no. 83379, Biological Abstracts, Inc., Philadelphia, PA, US; U.P. SINGH et al.: "The fungicidal effect of neem (Azadirachta indica) extracts of some soil-borne pathogens of gram (Cicer arietinum), & MYCOLOGIA 72(6): 1077-1093. 1980 * Abstract *	1-5,8,10, 11,13	
A	US-A-4 556 562 (R.O. LARSON)		TECHNICAL FIELDS SEARCHED (Int. Cl.5)

The present search report has been drawn up for all claims

Place of search	Date of completion of search	Examiner
The Hague	11 April 91	DONOVAN T.M.

CATEGORY OF CITED DOCUMENTS

X: particularly relevant if taken alone
Y: particularly relevant if combined with another document of the same catagory
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention

E: earlier patent document, but published on, or after the filing date
D: document cited in the application
L: document cited for other reasons

&: member of the same patent family, corresponding document

Extracts from
THE CONVENTION ON THE GRANT OF EUROPEAN PATENTS (EUROPEAN PATENT CONVENTION) of 5 October 1973

text as amended by the act revising Article 63 EPC of 17 December 1991 and by decisions of the Administrative Council of the European Patent Organisation of 21 December 1978, 13 December 1994, 20 October 1995, 5 December 1996 and 10 December 1998

PART II - SUBSTANTIVE PATENT LAW
CHAPTER I - PATENTABILITY

ARTICLE 52 - PATENTABLE INVENTIONS

(1) European patents shall be granted for any inventions which are susceptible of industrial application, which are new and which involve an inventive step.

(2) The following in particular shall not be regarded as inventions within the meaning of paragraph 1:

(a) discoveries, scientific theories and mathematical methods;

(b) aesthetic creations;

(c) schemes, rules and methods for performing mental acts, playing games or doing business, and programs for computers;

(d) presentations of information.

(3) The provisions of paragraph 2 shall exclude patentability of the subject-matter or activities referred to in that provision only to the extent to which a European patent application or European patent relates to such subject-matter or activities as such.

(4) Methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body shall not be regarded as inventions which are susceptible of industrial application within the meaning of paragraph 1. This provision shall not apply to products, in particular substances or compositions, for use in any of these methods.

ARTICLE 53 - EXCEPTIONS TO PATENTABILITY

European patents shall not be granted in respect of:

(a) inventions the publication or exploitation of which would be contrary to *ordre public* or morality, provided that the exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation in some or all of the Contracting States;

(b) plant or animal varieties or essentially biological processes for the production of plants or animals; this provision does not apply to microbiological processes or the products thereof.

ARTICLE 54 - NOVELTY

(1) An invention shall be considered to be new if it does not form part of the state of the art.

(2) The state of the art shall be held to comprise everything made available to the public by means of a written or oral description, by use, or in any other way, before the date of filing of the European patent application.

(3) Additionally, the content of European patent applications as filed, of which the dates of filing are prior to the date referred to in paragraph 2 and which were published under Article 93 on or after that date, shall be considered as comprised in the state of the art.

(4) Paragraph 3 shall be applied only in so far as a Contracting State designated in respect of the later application, was also designated in respect of the earlier application as published.

(5) The provisions of paragraphs 1 to 4 shall not exclude the patentability of any substance or composition, comprised in the state of the art, for use in a method referred to in Article 52, paragraph 4, provided that its use for any method referred to in that paragraph is not comprised in the state of the art.

ARTICLE 55 - NON-PREJUDICIAL DISCLOSURES

(1) For the application of Article 54 a disclosure of the invention shall not be taken into consideration if it occurred no earlier than six months preceding the filing of the European patent application and if it was due to, or in consequence of:

(a) an evident abuse in relation to the applicant or his legal predecessor, or

(b) the fact that the applicant or his legal predecessor has displayed the invention at an official, or officially recognised, international exhibition falling within the terms of the Convention on international exhibitions signed at Paris on 22 November 1928 and last revised on 30 November 1972.

(2) In the case of paragraph 1(b), paragraph 1 shall apply only if the applicant states, when filing the European patent application, that the invention has been so displayed and files a supporting certificate within the period and under the conditions laid down in the Implementing Regulations.

ARTICLE 56 - INVENTIVE STEP

An invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art. If the state of the art also includes documents within the meaning of Article 54, paragraph 3, these documents are not to be considered in deciding whether there has been an inventive step.

ARTICLE 57 - INDUSTRIAL APPLICATION

An invention shall be considered as susceptible of industrial application if it can be made or used in any kind of industry, including agriculture.

****

PART III - APPLICATION FOR EUROPEAN PATENTS

CHAPTER I - FILING AND REQUIREMENTS OF THE EUROPEAN PATENT APPLICATION

ARTICLE 75 - FILING OF THE EUROPEAN PATENT APPLICATION

(1) A European patent application may be filed:

(a) at the European Patent Office at Munich or its branch at The Hague, or

(b) if the law of a Contracting State so permits, at the central industrial property office or other competent authority of that State. An application filed in this way shall have the same effect as if it had been filed on the same date at the European Patent Office.

****

ARTICLE 78 - REQUIREMENTS OF THE EUROPEAN PATENT APPLICATION

(1) A European patent application shall contain:

(a) a request for the grant of a European patent;

(b) a description of the invention;

(c) one or more claims;

(d) any drawings referred to in the description or the claims;

(e) an abstract

****

ARTICLE 79 - DESIGNATION OF CONTRACTING STATES

(1) The request for the grant of a European patent shall contain the designation of the Contracting State or States in which protection for the invention is desired.

****

ARTICLE 80 - DATE OF FILING

The date of filing of a European patent application shall be the date on which documents filed by the applicant contain:

(a) an indication that a European patent is sought;

(b) the designation of at least one Contracting State;

(c) information identifying the applicant;

(d) a description and one or more claims in one of the languages referred to in Article 14, paragraphs 1 and 2, even though the description and the claims do not comply with the other requirements of this Convention.

ARTICLE 81 - DESIGNATION OF THE INVENTOR

The European patent application shall designate the inventor. If the applicant is not the inventor or is not the sole inventor, the designation shall contain a statement indicating the origin of the right to the European patent.

ARTICLE 82 - UNITY OF INVENTION

The European patent application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept.

ARTICLE 83 - DISCLOSURE OF THE INVENTION

The European patent application must disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

ARTICLE 84 - THE CLAIMS

The claims shall define the matter for which protection is sought. They shall be clear and concise and be supported by the description.

ARTICLE 85 - THE ABSTRACT

The abstract shall merely serve for use as technical information; it may not be taken into account for any other purpose, in particular not for the purpose of interpreting the scope of the protection sought nor for the purpose of applying Article 54, paragraph 3.

****

PART V - OPPOSITION PROCEDURE

ARTICLE 99 - OPPOSITION

(1) Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid.

****

ARTICLE 100 - GROUNDS FOR OPPOSITION

Opposition may only be filed on the grounds that:

(a) the subject-matter of the European patent is not patentable within the terms of Articles 52 to 57;

(b) the European patent does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art;

(c) the subject-matter of the European patent extends beyond the content of the application as filed, or, if the patent was granted on a divisional application or on a new application filed in accordance with Article 61, beyond the content of the earlier application as filed.

ARTICLE 101 - EXAMINATION OF THE OPPOSITION

(1) If the opposition is admissible, the Opposition Division shall examine whether the grounds for opposition laid down in Article 100 prejudice the maintenance of the European patent.

****

ARTICLE 102 - REVOCATION OR MAINTENANCE OF THE EUROPEAN PATENT

(1) If the Opposition Division is of the opinion that the grounds for opposition mentioned in Article 100 prejudice the maintenance of the European patent, it shall revoke the patent.

(2) If the Opposition Division is of the opinion that the grounds for opposition mentioned in Article 100 do not prejudice the maintenance of the patent unamended, it shall reject the opposition.

(3) If the Opposition Division is of the opinion that, taking into consideration the amendments made by the proprietor of the patent during the opposition proceedings, the patent and the invention to which it relates meet the requirements of this Convention, it shall decide to maintain the patent as amended, ……

****

PART VI - APPEALS PROCEDURE

ARTICLE 106 - DECISIONS SUBJECT TO APPEAL

(1) An appeal shall lie from decisions of the Receiving Section, Examining Divisions, Opposition Divisions and the Legal Division. It shall have suspensive effect.

****

ARTICLE 107 - PERSONS ENTITLED TO APPEAL AND TO BE PARTIES TO APPEAL PROCEEDINGS

Any party to proceedings adversely affected by a decision may appeal. Any other parties to the proceedings shall be parties to the appeal proceedings as of right.

****

FOREIGN AFFAIRS AND TRADE

AUSTRALIA

AusAID the Australian Government's overseas aid program

Module Six

Group exercise on patent validity: Relaxin patent

Intellectual Property and Biotechnology
A Training Handbook

Contents: Module Six

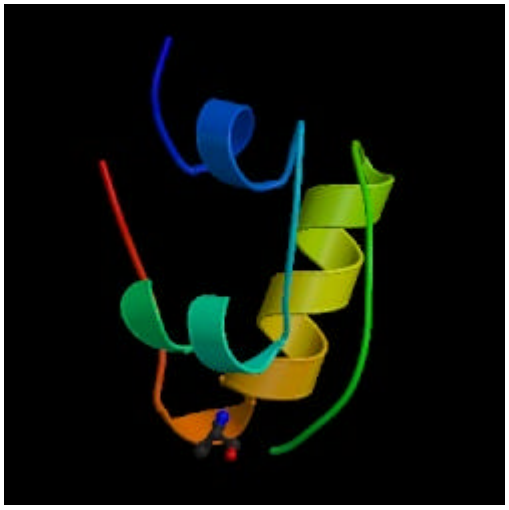
6.1 Objectives for Module Six

By the end of this Module you should have further practical experience in how to:

- apply the legal principles relating to the validity of complex biotechnology patents involving DNA sequences
- further explore the issues involved in assessing whether biotechnology inventions are patentable on the basis of:
  - novelty
  - inventive step
  - industrial application
  - usefulness
  - exceptions to patentability such as moral issues and *ordre public*
  - whether the claims are supported in the description

6.2 Background to the case study

This case study concerns important issues of patent validity, including consideration of the ethical issues related to the patent right. To set the patent documentation in context, we provide a discussion of some of the background to the invention. Patents, like other intellectual property rights, do not exist in isolation – they are part of a system intended to provide benefits for society. While this exercise concerns the strict legal validity of patents granted on the research outcomes, this exercise should also highlight potential benefits of a patent: in this case, the patent has the potential firstly to produce funds to pay for continuing valuable research, and secondly to provide the investor confidence required to go through the processes necessary to put a new pharmaceutical product on the market.

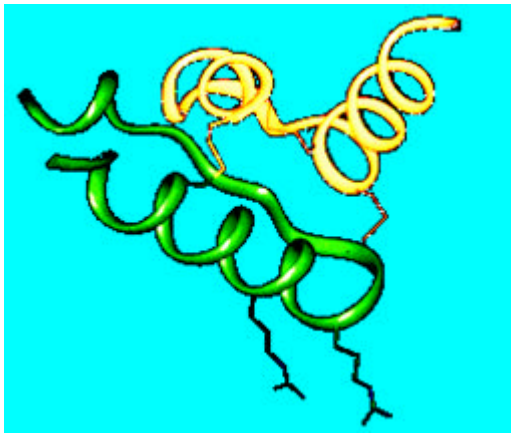


The case study concerns Relaxin, a synthetic peptide hormone. Hormones are normally produced naturally by plants and animals to regulate a wide range of bodily functions and to control the function of organs. Insulin and adrenaline are two examples of hormones, discussed in *Module Two*, which received patent protection in their synthesized form.

The synthesized relaxin was developed in the Howard Florey Institute, a medical research institute in Melbourne, Australia. Australian researchers have often taken a leadership role in their fields, but have generally been criticised for failing to manage their intellectual property to capture the benefits of their research. Relaxin is one example in Australia of effective intellectual property management, in which the IP has been appropriately protected and the licences have been able to return a reasonable royalty stream to support research work. Other related programs involved even more significant discoveries, but the IP was not adequately protected. So in once case, a nearby public research institute which undertook pioneering research into the GCSF and GMCSF growth factors found that the research led to the situation where a foreign pharmaceutical company was now reaping lucrative financial returns. This case demonstrated the need for effective IP management, to ensure that the products of research flow back to the country where the work has been done, but especially to the laboratories where the discovery was first made so that continuing valuable research can be funded.

At the same time, it can take a long time for basic research to lead into useful products. Relaxin has been a major research focus of the institute since 1975. The fruits of this research are only beginning to be realized. There is often a long delay from the breakthrough research phase to seeing a product on the marketplace: this is especially so for pharmaceuticals, for which the development and regulatory approval process is necessarily long. Considerable pressures can be felt during that period of delay: for instance, management may be under pressure to cut the costs for a project and to review expenditure such as patent fees, when a product is unlikely to return profits for some years. There is a continuing risk of cutting costs for short term gain while damaging longer-term interests.

Relaxin was first described in 1926, but it had been known for much longer that for a child to be born, the ligaments holding the pelvic bones together must change, as must the cervix itself which needs to soften and dilate in order to allow the baby to be born. It was clear that a specific hormone would perform this function. In 1926, a researcher took an extract of a pregnant guinea pig's ovaries. Introducing this into a guinea pig led to great relaxation of the pelvic bones. The chemical extract was called *relaxin* because of this relaxing effect on the ligaments. But the actual hormone was only isolated and its chemical structure determined in 1975, at the Howard Florey Institute (the patent applicant in this case study). This research was based on earlier work which established that the relaxin factor was produced in the ovaries during pregnancy. Based on analysis of discarded pigs' ovaries from an abbatoir, the material was isolated, extracted and purified. In tests, this material seemed to have all the biological properties of relaxin.



On further analysis, relaxin was determined to be a peptide (peptides are low-weight polymers of amino acids, in contrast to proteins which are larger and heavier polymers also made up of amino acids). Surprisingly, it was a two chain peptide (rather than the expected single chain structure), the two chains being joined by sulphide bridges – disulphide bonds. Also surprising was the fact that the hormone was analagous in its structure to insulin (even though the individual amino acids which made it up were different). Somehow relaxin and insulin were related to each other.

The research program then determined the structure of relaxin in many other mammals. It transpired that relaxin had evolved in different ways in each species – the only common element was the disulphide bonds. It was an important insight than only a few of the amino acids were important for the biological activity of relaxin. So the structure of relaxin was the same across species, while its specific composition differed by a few amino acids. It was therefore an important finding that only human relaxin would work on humans, and relaxin derived from other mammals would not be effective – unlike insulin (insulin from pigs had been used for many years to treat humans suffering from diabetes). As a result, to use relaxin to treat human diseases, it would be necessary to produce synthetic relaxin, rather than to rely on extracts from other species.

To make synthetic relaxin, it was necessary to determine its genetic sequence and to clone the gene through recombinant DNA techniques when they were just appearing. The researchers already had prior knowledge of relaxin in other species, so they were able to make the necessary probes and primers to extract the necessary findings for human relaxin. It was discovered that the gene coded not for two chains but the one chain. It emerged that there were actually two genes and two types of relaxin in the human (in contrast to the other animals). This research led to patent filings, first in Australia then in other countries.

Some of the biological actions of relaxin in the body are:

1. preventing the uterus from contracting
2. softening (ripening) the cervix at the time of birth to allow the child to pass through
3. effects on the heart
4. affecting mobility of sperm
5. blood pressure

For the first clinical application of sythentic relaxin, the researchers selected its used as a cervical ripening agent for post date (overdue) pregnancies. In the State of Victoria (where the Institute is located), 20% of all births were by caesariean section because of the post date problem, and using synthetic relaxin as a treatment offered a potential alternative to this kind of intervention. The necessary clinical trials turned out to be very expensive, and well beyond the means of the Institute. At this stage, the help of pharmaceutical companies was necessary. With the backing of the patent, the Institute tried to locate financial backers for this program. It proved impossible to get support from within Australia, and the patent was licensed to Genentech (see example in *Module Two*). Genentech funded the necessary clinical trials. The trial phase considered safety, the best method of application and the possibility of side effects. As this was a synthetic version of a natural hormone, side effects appeared unlikely in any case.

The next phase, the efficacy trial, commenced in 1992, when synthetic relaxin was first given to pregnant women. The method chosen was topical application – that is, to apply the synthetic relaxin directly by painting the cervix. There were no adverse side effects, but unfortunately nor was there any positive effect. This was a bad blow for the project at the time. It became clear later on that the problem was with the means of application – it would have been necessary to apply the relaxin intravenously. The effect at the time was that the financial backers asked to terminate the study, as several hundred million dollars had already been spent on the project. However, the team that had been working on the clinical trials and to develop the product decided to set up another company, Connective Therapeutics (now Connectics), to keep the work going. Genentech sublicensed the patent to this spin-off company to keep the project going. This led to change in direction.

Rather than consider the childbirth application (where medical litigation was a major risk), the project then looked at diseases associated with disorders in the connective tissue, for instance scleroderma ('hard skin'), a chronic and ultimately fatal disease caused by overproduction of collagen (a protein which forms fibres that are a major component of bones, tendons and other connective tissue). There was no treatment for scleroderma, which afflicted 300,000 patients in the US (80% of whom are women). Relaxin inhibits the production of collagen, and introducing synthetic relaxin proved to be the first effective treatment of scleroderma, which otherwise proved to be fatal. Relaxin has further potential applications in other disorders caused by fibrosis (the excessive growth of fibrous tissue) in the heart and liver, and also to prevent scar formation. The royalty from the relaxin patent was valuable in supporting continuing research into new clinical possibilities, and improved means of administering relaxin (which cannot be taken orally, because it is destroyed in the digestive tract).

The relaxin patent was approved by the European Patent Office (EPO) in 1992 – so the delay in patent approval was matched by the delays in the clinical program. However, the European patent was opposed by the Green Fraction of the European Parliament. This patent and opposition process forms the basis of this validity exercise. The opposition raised questions of ethics, novelty and non-obviousness, and proved to be a test case for the 'contrary to public order' provisions of European patent law.

6.3 Relaxin Patent Validity Exercise

How to undertake the case study

The following memoranda set out how the exercise can be conducted as a group exercise. A particular framework for this exercise is suggested, based on experience in using this exercise in practice. This material can be used in other ways, including for individual personal study. However, for the exercise to be effective, it would be useful to consider the issues at each stage only on the basis of the specific documents suggested for each role (described as Groups A, B, C and D). Memorandum A describes the suggested approach for managing a group exercise.

After the case study

While we recommend that it be set aside during the case study, the actual decision of the EPO is provided at the end of this Module, for cross-reference and to provide one perspective on the issues raised by this patent. The extract provided concentrates on the substantive patent law questions considered, and omits material on several other legal issues that were considered at the same time (essentially procedural questions, and questions of standing), although one other issue is still included – a challenge that the EPO dealt with the opposition in a partial manner.

MATERIALS

Memorandum A.	Explanation of the Validity Exercise (for Exercise Leader and Facilitators)
Memorandum B.	Information for the Introduction unit (for Exercise Leader and Facilitators)
Memorandum C.	Information for the Group Work unit (for Exercise Leader and Facilitators)
Memorandum D.	Information for the Group Report unit (for Exercise Leader and Facilitators)
Memorandum E.	Information for the Review unit (for Exercise Leader and Facilitators)
Memorandum F.	List of Materials issued to participants (for Exercise Leader and Facilitators)
Memorandum G.	Instructions for Group A
Memorandum H.	Instructions for Group B
Memorandum I.	Instructions for Group C
Memorandum J.	Instructions for Group D
Annexes	Reference documents

MEMORANDUM A.
EXPLANATION OF THE VALIDITY EXERCISE

1. What is the Validity Exercise?

The Validity Exercise is a role-playing exercise which forms part of a training program on biotechnology patents. The exercise is designed to enhance the learning of participants in relation to the legal and practical aspects of determining the validity of biotechnology patents. The exercise uses an actual application for a biotechnology patent ('the Application') and actual prior art and other documents involved in the prosecution of the Application before the European Patent Office. The exercise requires participants to carry out one of four roles, each of which is a simulation of an actual stage in the prosecution history of the Application.

The suggested approach to the exercise consists of four units, conducted over six sessions. The four units are as follows.

(i) Introduction unit

Exercise Leader explains to all participants the objectives and procedure of the exercise, and elaborates on and clarifies the technological and legal issues raised in the exercise.

(ii) Group Work unit

Each group carries out in parallel a different task which simulates one of the stages in the prosecution of the Patent.

(iii) Group Report unit

Each group reports in sequence to all participants on the outcomes of the task assigned to the group.

(iv) Review unit

Each exercise facilitator in sequence reviews the deliberations of their group in the Group Work unit, and comments on the outcomes of their group as reported in the Group Report unit.

2. Why have the Validity Exercise?

The Validity Exercise provides an opportunity for participants in the training program to apply in a practical context the abstract legal principles concerning the validity of biotechnology patents. The exercise thus provides a review and reinforcement of the legal principles which have been the subject of earlier instruction in the training program.

Because the exercise uses group work, each participant can benefit from the particular expertise, experience and insight brought to the training program by the other participants in the group. Further, the group work enables each participant to develop closer personal relationships with the other participants in the group, and to come to understand their perspectives on the issues raised by the exercise. Finally, the exercise provides an enjoyable and interactive set of sessions, and thus adds to the diversity of the learning formats adopted in the training program.

3. Who are the participants in the Validity Exercise?

The Validity Exercise involves the following participants.

(i) Exercise Leader

The exercise leader is one of the teachers on the training program. The exercise leader may also be one of the exercise facilitators. The exercise leader has responsibility for the overall conduct

of the exercise. In particular, the exercise leader is responsible for allocation of participants and exercise facilitators to particular groups and for the conduct of the introduction unit.

(ii) Group Members

Each participant is assigned to be a member of one of the four groups. The role of the group member is to work collaboratively with fellow group members, to carry out the task assigned to the group. Each group is responsible for determining how it will carry out the assigned task, and for carrying it out.

(iii) Exercise Facilitators

Facilitators may be teachers, practitioners or senior researchers with IP experience. Ideally, there will be four facilitators - that is, one for each of the four groups. Where necessary, however, it is possible to have only two facilitators. In that case, each facilitator assists two groups – that is, one facilitator for each pair of groups (i.e. Groups A/B and Groups C/D).

The role of the facilitator is two-fold. First, in the Group Work unit, the facilitator assists the group in carrying out the assigned task. In particular, the facilitator may need to clarify the precise nature of the assigned task, and help the group with understanding the application of the law to the particular facts of the task. Secondly, in the Review unit, the facilitator provides a review of the deliberations undertaken by the group in the Group Work unit, and comments on the Report given by the group in the Group Report unit. The facilitator is not responsible for carrying out the work of the group.

4. How are members allocated to groups?

The exercise leader should allocate participants to one of the four groups in advance of the exercise, so that they can undertake informal preliminary discussions with their fellow group members. So far as practicable, the allocation should ensure that, across the four groups, each group has:

- an equal number of participants
- a consistent proportion of participants from similar backgrounds (e.g. from law, science, administration, policy) – it is particularly valuable if the groups can combine people with backgrounds in scientific research and in intellectual property law and administration
- a consistent proportion of men and women
- where relevant, a consistent proportion of participants from different countries and/or geographical regions

5. What is the suggested schedule for the exercise?

The exercise is ideally conducted over six sessions. There should be a break (either in the form of a short refreshment break or a break between days of the training program) after the second, fourth and six sessions. Optionally, there may be a break between the first and second sessions.

The suggested order, content and approximate duration of each session is set out below.

Session	1	2	3	4	5	6
Unit	Introduction	Group Work	Group Report	Review	Group Report	Review
Groups	All	All	A and B	A and B	C and D	C and D
Duration	30 mins	75 mins	45 mins	45 mins	45 mins	45 mins

MEMORANDUM B.
INFORMATION ABOUT THE INTRODUCTION UNIT

1. The Purpose of the Introduction Unit

The purpose of the Introduction unit is to ensure that all participants understand:

- the objectives and the process of the exercise
- the role of the group members and of the exercise facilitators
- the facts of the exercise, including a basic understanding of the technology of the Patent
- the task of each group, including the particular legal issues and the basics of the legal principles which apply to the task

The Introduction unit should be conducted by the exercise leader, in the presence and with the assistance of the exercise facilitators. It should allow plenty of scope for all participants to ask questions about the exercise.

2. The Objectives and Process of the Exercise

The exercise leader should explain that the exercise seeks to achieve a number of objectives. In particular, the exercise provides a practical context in which participants are able to apply the legal principles of the validity of biotechnology patents. The exercise thus provides an opportunity for participants to review their knowledge of those legal principles, and reinforce their understanding of how those legal principles apply in practice.

The exercise leader should emphasise that the purpose of the exercise is not to assess or evaluate the participants' learning to date, but rather to provide a different and enjoyable means for continuing the participants' learning. The questions are not to be answered in true/false fashion, but to be used as the basis for a discussion on the nature of the issues involved.

The exercise leader should describe the schedule of the exercise. In doing so, the exercise leader could explain that the tasks constitute a simulation of four stages in the prosecution of an actual patent, and that these task fall into two pairs – those of Groups A and B, and those of Groups C and D. Accordingly, the Group Report and the Review of Groups A and B should take place before the Group Report and the Review of Groups C and D.

3. The Role of the group members and the facilitators

The exercise leader should explain that the responsibility for determining how to conduct the task, and for conducting the task, rests with the group members. There is no prescribed or preferred method for undertaking the task, and different groups may approach their tasks in quite different manners. For example, some groups may allocate specific questions or issues to individual group members, whilst other groups may seek to answer all questions or issues collectively – both approaches are equally valid. Likewise, it is equally valid for a group to appoint one member as its spokesperson during the Report unit or instead for a group to have a number of its members speak during the Report unit.

The exercise leader should emphasise that the role of the exercise facilitator is to assist the group in clarifying their understanding of facts and of the legal issues raised in the task. It is not the responsibility of the facilitator to tell the group how to carry out the task, or to carry it out for them.

4. The Invention considered in the exercise

The exercise leader should explain that the exercise focuses on the various stages of prosecution of an application for a patent for an actual invention ('the Invention') before the European Patent Office ('EPO'). The application for the patent ('the Application') is European Patent Application no. 83307553.4 (Document 2 in the Materials issued to participants). The Application was filed in the EPO on 12 December 1983, and claimed priority from an application for the same invention filed in the Australian Patent Office on 13 December 1982.

The Invention was selected for use in the exercise for a number of reasons. First, the Invention is reasonably representative of one of the types of biotechnology inventions for which patents are sought. Secondly, the particular nature of the Invention raises some very interesting and contentious patent issues, both legal and non-legal. Thirdly, the form and content of the Application is reasonably representative of biotechnology patent applications of this type. (It may be noted, in addition, that because the Application was one of the earlier applications made for molecular cloning using recombinant DNA technology, it contains some useful basic information about recombinant DNA technology that is not generally found in later patent applications for this type of biotechnology invention.)

The Invention relates to the discovery of a gene which encodes for the production of a hormone, relaxin, in humans. In fact, as the Application itself states (p. 1), the Invention concerns the discovery of a second gene encoding for a second human relaxin protein (H2-relaxin). As stated in the Application (p. 3), relaxin is a hormone produced in mammals, which has the effect of dilating the pubic symphysis, thus making childbirth easier. It is produced by the ovaries during pregnancy, and released into the blood stream during labour.

The Application states (pp 3-4) that there has already been determined the amino acid sequence for relaxin in pigs, rats and sharks, and the amino acid sequence of and the DNA nucleotide sequence encoding for a first human relaxin protein (H1-relaxin). The similarities and differences between H1-relaxin and H2-relaxin are described in the Application (pp 8-11).

The Application proceeds to describe in some detail the various aspects of the Invention (pp 12-21), which are reflected in the claims at the end of the specification (pp 42-49). The aspects of the Invention are:

- genes for the expression of H2–preprorelaxin, prorelaxin and relaxin, and polymorphic forms, complements, sub-units and variants thereof (pp 12-14)
- DNA transfer vectors comprising the deoxynucleotide sequence corresponding to these genes (pp14-15)
- a prokaryotic or eukaryotic cell transformed by any of these transfer vectors (p. 15)
- processes for making these DNA transfer vectors, for making a fusion protein by incubating a cell culture transformed by an expression transfer vector prepared by that process, and for synthesizing H2 preprorelaxin, prorelaxin and relaxin therefrom (pp 15-18)
- human relaxin analogues and processes for production thereof (pp 18-21).

The Application then sets out the methods and materials by which these aspects of the Invention were made (pp 22-39), and a list of references (pp 40-41).

The Application concludes with the claims (pp42-49). There are 32 claims, each of which relates to a different aspect of the Invention, in accordance with the preceding description (pp12-21). The claims are followed by five figures (1/5-5/5), which are referred to in the preceding description of the Invention.

5. The jurisdiction and relevant legislation

Prosecution before the EPO was chosen for the exercise because the relevant law is conveniently contained in the European Patent Convention ('EPC'). A large number of European countries are members of the EPC. Extracts of the relevant provisions from the EPC are in Document 1 in the Materials issued to the participants.

The relevant provisions of the EPC are expressed in reasonably simple and clear terms, and are generally representative of the law of patent validity as it applies throughout the world. Some of the provisions of the EPC (namely those dealing with the exceptions to patentability) do not have direct counterparts in other countries' legislation. Nevertheless, the issues to which those provisions relate are fundamental to all patent laws. Also, similar provisions are found in the TRIPS Agreement (arts 27(2) and (3)) as optional exceptions to patentability.

The legislation extracts contain provisions from Parts II, III, V and VI of the EPC. The basic effect of the key provisions are as follows.

Part II – Substantive Patent Law

Article 52 – Patentable inventions:

- art. 52(1) sets out the basic requirements for the grant of a valid patent –*i.e.* an invention, industrial applicability, novelty, and inventive step
- arts 52(2)-(4) deals with inherently unpatentable subject matter –*i.e.* subject matter which is not an invention or which is incapable of industrial application

Article 53 – Exceptions to patentability:

- art. 53(a) excludes inventions that are contrary to public policy or morality
- art. 53(b) excludes inventions concerning plant and animal varieties and essentially biological processes for their production

Article 54 – Novelty:

6. art. 54(1) sets out the test for novelty –*i.e.* the invention does not form part of the state of the art
7. arts 54(2)-(5) describe the state of the art against which novelty is tested –*i.e.* everything made available to the public before the date of filing of the application, plus other European patent applications with an earlier filing date that are published after the date of filing of the application

Article 55 – Non-prejudicial disclosures:

- prescribes disclosures of the invention which are disregarded when testing for novelty –*i.e.* disclosures less than six months before the date of filing which result from an abuse of the applicant or from display at an officially recognised international exhibition

Article 56 – Inventive step:

- sets out the test for the presence of an inventive step –*i.e.* the invention is not obvious to a person skilled in the art, having regard to the state of the art

Article 57 – Industrial application:

- sets out the test for industrial applicability –*i.e.* it can be made or used in any kind of industry

Part III – Application for European Patents

Article 78 – Requirements of the European Patent Application:

- sets out what an application for a patent must contain –*i.e.* a request for grant, a description of the invention, one or more claims, any drawings referred to in the description or the claims, and an abstract

Article 82 – Unity of invention:

- requires that the patent application relate to one invention only

Article 83 – Disclosure of the invention:

8. requires that the application clearly and completely disclose the invention

Article 84 – The claims:

- requires that the claims define the invention, are clear, are concise and are supported by the description

Part V – Opposition Procedure

Article 100 – Grounds of opposition:

- sets out the grounds on which an opposition to the grant of a patent may be filed –*i.e.* the subject matter is not patentable within the terms of EPC arts 52-57, the patent does not disclose the invention sufficiently, and the subject matter extends beyond the content of the application

5. The tasks of each group

The leader should explain that each group has been given a different task, where each task represents one of the actual stages in the prosecution of the application for a patent for the Invention. The four tasks are as follows.

Group A:
Group A acts as an Examiner in the European Patent Office, in the Biotechnology section. The group is required to examine the Application for compliance with the provisions of the EPC dealing with Patentability and Filing Requirements –*i.e.* under Chapter I of Part II and Chapter I of Part III. In particular, the group is to determine the extent to which the Application satisfies these requirements.

Group B:
Group B acts a European Patent Attorney, specialising in biotechnology patents. The group is required to prosecute the Application before the EPO. In particular, the group is to provide a Response to the first substantive Examination Report of the Examining Division of the EPO.

Group C:
Group C is the European Green Party. The group is required to oppose the grant of the patent for the Invention. In particular, the group is to prepare the Grounds of Opposition, for filing in the EPO prior to the Opposition hearing.

Group D:
Group D acts a European Patent Attorney, specialising in biotechnology patents. The group is required to defend the Opposition to the grant of a patent for the Invention, lodged by the European Green Party. In particular, the group is to prepare the Reply to the Opposition, for filing in the EPO prior to the Opposition hearing.

MEMORANDUM C.

INFORMATION FOR THE GROUP WORK UNIT

1. The purpose of the Group Work Unit

The purpose of the Group Work unit is to provide the participants with an opportunity to apply in a practical context the abstract legal principles relating to the validity of biotechnology patents. In particular, the participants are provided with the opportunity to benefit from the expertise and experience of their fellow group members in dealing with a practical task. This constitutes an important part of the learning process, because the practical task involves complex issues of law and of technology, being issues which benefit from a multi-disciplinary perspective.

2. Task of Group A

Group A acts as an Examiner in the European Patent Office ('EPO'), in the Biotechnology section. The group is required to examine European Patent Application no. 83307553.4 ('the Application') for compliance with the provisions of the European Patent Convention ('EPC') dealing with Patentability and Filing Requirements –*i.e.* under Chapter I of Part II and Chapter I of Part III. Relevant extracts of the EPC are in Document 1, and a copy of the Application is Document 2, in the Materials provided to participants.

The group is provided with two pieces of prior art, found as a result of the Search conducted by the EPO Search Division. These are an article in the scientific journal *DNA* (Document 3 in the Materials) and a published application for another European Patent (Document 4 in the Materials). The group is to assume that these two documents are the only relevant documents found as a result of that search.

The task of the group is to determine the extent to which the Application satisfies these requirements. In doing so, the group is required to answer the following specific questions:

1. Do all the claims satisfy article 52(1) –*i.e.* are they for an invention that:
   (a) is novel, under articles 54 and 55?
   (b) involves an inventive step, under article 56?
   (c) is capable of industrial application, under article 57?
2. Are any of the claims excluded by article 52(2)(a) –*i.e.* are they discoveries?
3. Are any of the claims excluded by article 52(4) –*i.e.* are they for methods for treatment of the human body by surgery or therapy?
4. Are any of the claims excluded by article 53(a) –*i.e.* are they contrary to "ordre public" or morality?
5. Do the claims satisfy article 82 –*i.e.* do they relate only to one invention or inventive concept?
6. Do the claims satisfy article 84 –*i.e.* are they clear and concise and supported by the description?

Question 1(a):
This requires a comparison between each claim of the Application and what is disclosed in the state of the art. A claim will not be novel if it relates to subject matter which is disclosed in the state of the art. Are either of the two documents part of the state of the art? Is the subject matter of any claim disclosed in the state of the art?

Question 1(b):
This requires a consideration of whether the subject matter of each claim is obvious to a person skilled in the art, having regard to the state of the art which may be considered for inventive step. Are either of the two documents part of the state of the art for inventive step? What type of person is skilled in this art? What would be obvious to that type of person?

Question 1(c):
This requires a consideration of whether the subject matter of each claim is capable of being made or used in any kind of industry. What is an "industry". Is there an industry in which the subject matter of each claim can be made or used?

Question 2:
This requires a consideration of what is a "discovery", and also of what is the meant by the "as such" qualification imposed by article 52(3). Is the H2 gene naturally occurring? If so, does that make the claims to it a discovery as such? Does disclosing the DNA and amino acid sequences make the claims to subject matter more than a discovery *as such*?

Question 3:
This requires a consideration of what is a method for the treatment of the human body by surgery or therapy. Does this include subject matter that may be used or involved in such a treatment?

Question 4:
This requires a consideration of what is meant by "ordre public" and what is "contrary to law". How is the relevant public policy/policies to be identified? Are there policies in favour of granting the patent? In relation to what law(s) might the invention be contrary?

Question 5:
This requires a consideration of what is the inventive concept(s) disclosed in the Application, and an analysis of whether the claims relate to only one such concept. How might the Invention disclosed in the Application be conceptualised?

Question 6:
This requires an analysis of whether there is any ambiguity or lack of definition of subject matter in each claim. What is the subject matter of each claim? Has it been adequately defined?

3. Task of Group B

Group B acts a European Patent Attorney, specialising in biotechnology patents. The group is required to prosecute the Application before the EPO.

The group is provided with the first substantive Examination Report of the EPO (Document 5 in the Materials). The Examination Report considers the extent to which the Application complies with provisions of the EPC dealing with Patentability and Filing Requirements –*i.e.* under Chapter I of Part II and Chapter I of Part III. The Examination Report refers to, and the group is supplied with a copy of, a published application for another European Patent (Document 4 in the Materials).

The task of the group is to provide a Response to the first substantive Examination Report. In doing so, the group is required to answer the following specific questions:

1. Are the following objections raised in the Examination Report valid:
   (a) the claims lack unity under article 82 –*i.e.* there are three separate inventions, being claims 1-23, claims 24-29 and claims 30-32?
   (b) the claims (inc. claim 1) which refer to "H2-preprorelaxin" per se lack clarity under article 84 –*i.e.* they do not identify the specific structural features which distinguish between H1, H2 and known human relaxin?
   (c) the claims (inc. claim 1) which refer to "or a sub-unit thereof" lack clarity under article 84 and novelty under article 54 –*i.e.* they are not clearly distinguished from certain of the claims in the earlier European Patent Application publication no. 0,101,309 for H1 relaxin?
2. What amendments, if any, should be made to the Application in light of these objections?

Questions 1(a) and 2:
This requires a consideration of whether or not the three groups of claims relate to the one inventive concept. How should the Invention disclosed in the Application be conceptualised? For instance, what is the technical problem it addresses, and how does it solve that problem? Is there an inventive concept to which more than one of the three groups of claims relate?

Question 1(b) and 2:
This requires an analysis of whether the claims sufficiently describe the subject matter. What is the subject matter of the claims being challenged on this ground? How can and should that subject matter be defined?

Question 1(c) and 2:
This requires an analysis of whether the claims cover subject matter that is disclosed in the H1-relaxin patent application. What is disclosed in the H1-relaxin patent application? Does a claim to a sub-unit of the H2-relaxin gene cover that disclosure? If it does, should these parts of the claims be deleted? What would be the effect of such a deletion on the scope of the claim?

4. Task of Group C

Group C is the European Green Party. The group is required to Oppose the decision of the EPO to grant a patent for the Invention.

The Application was accepted by the EPO, after amendment by the applicant, to become European Patent no. 0,112,149 ('the Patent'). A copy of the Patent (Document 7 in the Materials) is provided to the group. The group is also provided with a copy of an article in the *New Scientist* magazine (Document 6 in the Materials), which states that the Green Party has opposed the grant of the Patent.

The task of the group is to prepare the Grounds of Opposition, for filing in the EPO prior to the Opposition hearing. In doing so, the group is required to answer the following specific questions:

1. Is it feasible to oppose the grant of the Patent on any of the following grounds –*i.e.* that the invention:
   (a) is not capable of industrial application, under article 52(1)?
   (b) is excluded as a discovery, under article 52(2)(a)?
   (c) is excluded as contrary to "ordre public" or morality, under article 53(a)?
   (d) is not novel, under article 54?

(e) does not involve an inventive step, under article 56?

2. If so, what arguments would you make in support of those grounds?

Question 1(a) and 2:
This requires a consideration of whether the subject matter of each claim is capable of being made or used in any kind of industry. What is an "industry"? Is there any industry in which the subject matter of each of the claims of the Patent may be made or used?

Question 1(b) and 2:
This requires a consideration of what is a discovery, and also of what is the meant by the "as such" qualification imposed by article 52(3). Is the H2-relaxin gene naturally occurring? If so, does that make the claims to it a discovery as such? Does disclosing the DNA and amino acid sequences make the claims to subject matter more than a discover as such?

Question 1(c) and 2:
This requires a consideration of what is meant by "ordre public" and what is "contrary to law". How is the relevant public policy/policies to be identified? Are there policies in favour of granting the patent? In relation to what law(s) might the invention be contrary?

Question 1(d) and 2:
This requires a comparison between each claim of the Application and what is disclosed in the state of the art. A claim will not be novel if it relates to subject matter which is disclosed in the state of the art. What comprises the state of the art? Is the H2-relaxin gene in humans part of the state of the art?

Question 1(e) and 2:
This requires a consideration of whether the subject matter of each claim is obvious to a person skilled in the art, having regard to the state of the art which may be considered for inventive step. What type of person is skilled in this art. What would be obvious to that person?

5. Task of Group D

Group D acts a European Patent Attorney, specialising in biotechnology patents. The group is required to defend the Opposition to the grant of a patent for the Invention, lodged by the European Green Party.

The group is provided with a copy of the Patent –*i.e.* the Application as accepted by the EPO, after amendment by the applicant (Document 7 in the Materials). It is also provided with the Grounds of Opposition filed by the Green Party (Document 8 in the Materials).

The task of the group is to prepare the Reply to the Opposition, for filing in the EPO prior to the Opposition hearing. In doing so, the group is required to answer the following specific questions:

1. How should you respond to the technical and legal arguments contained in Parts I and II of the Opposition –*i.e.* the arguments that the invention:
   (a) is excluded as a discovery, under article 52(2)(a)?
   (b) is not novel, under article 54?
   (c) does not involve an inventive step, under article 56?

2. How should you respond to the morality arguments contained in Parts III and IV of the Opposition -*i.e.* the arguments that the invention is excluded as contrary to "ordre public" or morality, under article 53(a)?

Question 1(a) and 2:
This requires a consideration of what is a "discovery", and also of what is the meant by the "as such" qualification imposed by article 52(3). Is it true to say that claims 1-4 are "described solely in respect of their ability to code" and that "there is no reference whatsoever to their chemical composition"? What is meant by the last paragraph under heading I?

Question 1(b) and 2:
This requires a comparison between each claim of the Application and what is disclosed in the state of the art. What forms part of the state of the art? Is the H2-relaxin gene in the tissue of pregnant women part of the state of the art? Does "isolating" and "purifying" the gene change the situation? Is it true to say that "the elucidation of the chemical structure has no patentability, because it is effected in conventional manner known per se"?

Question 1(c) and 2:
This requires a consideration of whether the subject matter of each claim is obvious to a person skilled in the art, having regard to the state of the art which may be considered for inventive step. What type of person is skilled in this art? What would be obvious to that person? What is the inventive step here? Does the fact that "the structural analyses … are carried out by machine" mean there can be no inventive step?

Question 2:
Does the fact that tissue was taken from pregnant women offend against public morality. What is the relevance of the taking being for profit? Does the patent give "private ownership" to a gene? If so, does this "disgust" or offend the dignity of man? Does an observance of article 53(a) require the EPO to make enquiries in each member state as to what is contrary to public order and morality? Is there any public policy in favour of the grant of the Patent?

MEMORANDUM D.
INFORMATION FOR THE GROUP REPORT UNIT

1. The purpose of the Group Report Unit

The purpose of the Group Report unit is two-fold. First, it provides a focus for the deliberations carried out in the Group Work unit. Knowing that a Report is required gives motivation and context for attempting to answer the questions raised by the task. Secondly, a Report by each group provides important information to the members of the other groups. In this way, participants get to learn about the issues and answers involved in tasks other than the one carried out in their group. Having other participants deliberate on and then report about a set of issues is an effective and efficient way of sharing the learning.

2. The role of the group members

The role of the group members is to provide a clear and succinct oral report of how the group tackled the task, and of the outcomes of their deliberations. This may be done in a number of equally appropriate ways. For example, a group may appoint one spokesperson to provide the Report. Alternatively, a number of the group members may be involved in providing the Report.

The Report should explain the approach adopted to answering each question, the answer to each question, and the reasons for this answer. For example, in relation to a question concerning novelty, the Report should (briefly) identify the provisions of the legislation which are relevant (i.e. article 54), determine whether the documents provided are part of the state of the art, ascertain what is disclosed by the state of the art, compare this with the subject matter of each claim, and draw a conclusion about whether or not each claim is novel.

3. The role of the exercise facilitators

The role of the exercise facilitator during the Group Report unit is limited. If necessary, the facilitator might need to prompt the group to respond to a specific question or issue comprised in the task, or to clarify a statement by the group. The facilitator has the opportunity to comment on, and if necessary correct or expand on, the report of the group during the Review unit which follows.

MEMORANDUM E.

INFORMATION FOR THE REVIEW UNIT

Please note: this document provides comment on the substantive legal questions to facilitate the review of the exercise. This information should not be used prior to the group exercises themselves, as it would reduce the value of the groups' own analysis of the issues. These comments are provided at this stage to help ensure that the discussion is focussed and comprehensive.

For further reference, Document 9 in the attached documentation is a copy of the actual decision delivered by the European Patent Office in the Relaxin opposition case. It is suggested that this is consulted and discussed ***after*** the validity exercise and the review unit.

1. The purposes of the Review Unit

The Review unit provides an opportunity for facilitators to give feedback to the participants on the discussions in the Group Work unit, and on the conclusions they report. It also allows participants to ask questions, and make comments, on any aspect of any of the tasks, either of their own group of some other group. The Review unit can assist in clarifying and revising the legal principles on the validity of biotechnology patents. It is also an opportunity to analyse the different approaches which might be adopted in applying these principles in practice, in particular to consider how they might be applied differently in other countries.

Set out below are some comments on each of the specific questions dealt with by the groups. To the extent to which a group did not address one of these questions, or addressed it in a different manner, the group facilitator can use these comments as the basis for further instruction on that issue.

These comments do not represent a definitive or authoritative answer on any of these issues under European or any other laws, but are provided to stimulate further discussion. The review process might also discuss whether the rules are likely to be different, or be applied differently, in other countries, for example countries in the Asia Pacific region.

2. Comments on the Task of Group A

Question 1(a):

- In general terms, the Invention is novel.
- The *DNA* article is part of the state of the art for determining novelty, because it was published on a date (24 August 1982) before the deemed date of filing (which is the priority date, pursuant to article 89) of the Application (13 December 1982, the date of the Australian application).
- The application for the H1-relaxin patent is also part of the state of the art for determining novelty, even though it was published on a date (22 February 1984) ***after*** the deemed date of filing of the Application. This is because its deemed date of filing (12 August 1982) is before the deemed date of filing of the Application, and so it forms part of the state of the art unde r article 54(3).
- Neither document discloses H2-relaxin or the gene for it.

- The article from the journal *DNA* is concerned with porcine relaxin. It discloses the DNA sequence for the porcine gene for relaxin and the amino acid sequence of porcine relaxin. These sequences differ in significant ways from the DNA and amino acid sequences for H2-relaxin claimed in the Application.
- The H1-relaxin patent discloses the DNA and amino acid sequences for H1-relaxin. Whilst there is a close degree of similarity between these sequences and the respective sequences claimed in the Application, nevertheless there are important differences. The Application identifies these differences.
- There are some individual claims in relation to which it can be argued there is a lack of novelty.
- Claim 1 refers to 'a sub-unit' or 'an equivalent' of the gene for H2-preprorelaxin. Certain parts of the H1-relaxin gene would be a sub-unit, and might be an equivalent, of the H2-preprorelaxin gene. Accordingly, those sub-units and equivalents are disclosed in the state of the art.
- Thus, claim 1, and any claim dependent on it (eg. claims 3 and 5) or drafted like it (eg. claim 7) is not novel.

Question 1(b):

- In general, the Invention involves an inventive step.
- The *DNA* article is part of the state of the art for determining inventive step, but the H1-relaxin patent application is not. This is because article 56 excludes documents within the meaning of article 54(3) – the H1-relaxin patent application had not been published at the priority date of the present patent application.
- The *DNA* article does not disclose, or suggest, that there is an H2-relaxin gene. More significantly, the *DNA* article does not disclose, or suggest, what is the DNA and/or amino acid sequence of the H2-relaxin.
- Similar to the situation with respect to novelty, it may be argued that claim 1 (and any dependent or similar claim) lacks an inventive step, because the state of the art discloses sub-units and/or equivalents of the gene for H2-preprorelaxin.

Question 1(c):

- In general terms, the Invention claimed in the Application is capable of industrial application.
- The Invention can be made or used in an industry. For example, knowledge of the DNA and amino acid sequences, and in particular how to synthesise them, may be used to produce synthetic compounds for administration to humans.

Question 2:

- In general terms, the Invention is not a discovery as such.
- The Application goes beyond disclosing the existence of H2-relaxin, and in particular discloses the DNA and amino acid sequences of H2-relaxin, thereby providing a means by which H2-relaxin can be synthesised. Synthesised H2-relaxin is not a naturally occurring substance.
- There are some individual claims which it can be argued are for a discovery as such.
- Claim 1 (and any dependent or similar claim) is for a discovery as such, because it does not identify the DNA or amino acid sequences of H2-preprorelaxin.

Question 3:

- None of the claims are for methods for treatment of the human body by surgery or therapy.

- Although the Invention is likely to lead to therapies for treating the human body, the claims themselves are not for any such treatment. The claims are limited to genes, transfer vectors, transformed cells, and production processes for certain of those subject matters.

Question 4:

- The claims do not seem to be contrary to "ordre public" or contrary to law.
- It does not seem possible to identify a public policy which is breached by the Invention.
- Also, it seems possible to identify a public policy in favour of the Invention – *eg* the relief of suffering during childbirth, and the production of new products for treating other diseases.

Question 5:

- It is arguable that the claims relate to more than one invention or inventive concept.
- It may be argued that the claims relating to H2-relaxin and production processes therefor are for an invention different from that claimed in the claims relating to H2-relaxin analogues and the processes for their production.

Question 6:

- Generally, the claims are clear and concise.
- It may be argued that claim 1 (and any dependent or similar claim) is not clear, because it does not specify the DNA and amino acid sequences for H2-relaxin.

3. Comments on the Task of Group B

Questions 1(a) and 2:

- The objection of lack of unity of invention arguably results from too strict an application of the principle.
- It is arguable that there is one general inventive concept disclosed in the Application – the DNA and amino acid sequences of H2-relaxin – and that all the claims relate to this one inventive concept.
- If this argument is not persuasive, the Application should be amended by deleting claims 24-29 and claims 30-32. Two further applications, one for each of these groups of deleted claims, could be made, each claiming a priority date the same as that of the Application.

Question 1(b) and 2:

- The objection of lack of clarity of some claims seems valid.
- Claim 1, and any claim dependent on it (eg. claims 3 and 5) or drafted like it (eg. claim 7), refers to 'a gene for the expression of human H2-preprorelaxin', but it does not identify the sequence of the gene or of H2-preprorelaxin. The claim (and any dependent or similar claim) thus could fail to properly define the subject matter for which protection is sought (and arguably also is for a discovery as such, and is not capable of industrial application).
- Claim 1 (and any dependent or similar claim) should be amended, so as refer to DNA encoding for a particular amino acid sequence, and the amino acid sequence should be set out in the claim.

Question 1(c) and 2:

- The objection of lack of novelty of some claims seems valid.
- Claim 1, and any claim dependent on it (eg. claims 3 and 5) or drafted like it (eg. claim 7), refers to 'a sub-unit' or 'an equivalent' of the gene for H2-preprorelaxin. Certain parts of the

H1-relaxin gene would be a sub-unit, and might be an equivalent, of the H2-preprorelaxin gene. Accordingly, those sub-units and equivalents are disclosed in the state of the art.

- The claim (and any dependent or similar claim) thus lacks novelty.
- The claim (and any dependent or similar claim) should be deleted.

4. Comments on the Task of Group C

Question 1(a) and 2:

- There is arguably some ground, albeit slight in substance, for saying that there is no "industry" in which the subject matter of the claims of the Patent can be made or used.
- This argument addresses the fundamental issue of what is an "industry". It might be argued that an "industry" is something in which a practical application of the invention can occur, where such application is of economic, as distinct from say intellectual or theoretical, significance.

Question 1(b) and 2:

- The argument that the Invention is a discovery is a stronger ground of opposition.
- It can be argued that the claims to DNA fragments are claims to a discovery as such. This argument deals with the fundamental issues of what is a "discovery", and of what is the meant by the "as such" qualification imposed by article 52(3).
- It can be argued that the DNA fragment is naturally occurring, and all the patentee has done is discover the sequence of it. Merely identifying and disclosing the composition of a naturally occurring molecule is not sufficient to warrant the grant of a patent for the molecule.

Question 1(c) and 2:

- It is difficult to identify any law to which the grant of the Patent would be contrary.
- There is more scope for arguing that the grant of the Patent is contrary to "ordre public".
- It might be said that genes are naturally occurring subject matter which should not be capable of being owned by anyone. Reference to the fact that genes are the biological building blocks of human beings might support this assertion.

Question 1(d) and 2:

- It could be argued that the subject matter of the DNA fragment claims, and of related claims, are not novel because they concern material that is already in existence. Pre-existing material should not be considered new.
- It is harder to make this argument in relation to the claims dealing with synthesised DNA fragments.
- The process claims seem to have novelty.

Question 1(e) and 2:

- There is some ground for arguing that the Invention lacks an inventive step.
- It could be argued that it would be obvious to a person skilled in the art that it would be desirable to identify the sequence of a (second) gene for relaxin in humans, and that given the state of the art about relaxin, it would be obvious to proceed to identify that sequence.
- It might be said that all the patentee has done is apply known and obvious techniques to achieve an obviously desirable piece of information.

5. Comments on the Task of Group D

Question 1(a):

- The claims which refer to the DNA fragments by their ability to encode for a particular amino acid are for more than a discovery as such.
- These claims indirectly described the sequence of the DNA fragments, because a person skilled in the art would know, and the patent specification itself states, which codons code for which amino acids.
- These claims are to more than a discovery as such. They are claims to subject matter which has a particular, and described, chemical composition.

Question 1(b):

- It can be said that the claimed subject matter lacks novelty only if it has previously been "made available to the public".
- The fact that the H2-relaxin gene and H2-relaxin were pre-existing, by virtue of being in the human body, does not mean they had been made available to the public. That is to say, there has been no making available to the public, by written or oral disclosure, by use, or in any other way, of H2-relaxin or the gene encoding for it.
- Also, the main claims are not to the H2-relaxin gene, but to DNA fragments encoding for the production of H2-relaxin. These fragments are not the same as the gene for H2-relaxin, because they do not include introns (non-coding sequences which are present in the natural DNA).
- The claims to the DNA fragments, and the rest of the claims, are thus novel.
- The DNA fragments were not "isolated and purified". Rather, the mRNA was determined, the DNA cloned and recombinant technology used to produce H2-relaxin.

Question 1(c):

- There were no disclosures in the state of the art which suggested or made obvious the existence of a second human relaxin protein and thus a gene therefor.
- The inventive step was to ascertain that there was a second human relaxin protein.
- The use of automated processes for determining the chemical structure of the DNA fragments does not change the fact that there was an inventive step. The chemical structure could not have been determined without first knowing of the existence and amino acid sequence of the second human relaxin protein.

Question 2:

- The grant of the Patent does not have the effect of transferring a gene to private ownership. The H2-relaxin gene is not owned by anyone. Rather, the Patent grants limited exclusive rights to certain subject matter (DNA fragments) and processes which were not known, and which did not exist, prior to the making of the Invention.
- The grant of the Patent has not been shown to be contrary to any law.
- The grant of the Patent is beneficial to society in a number of respects. The Patent discloses information that can be used to produce synthetic therapeutic compounds, which provide relief from suffering during childbirth and have other therapeutic benefits.

For further study

After the exercise, training participants may like to read the actual decision delivered by the European Patent Office in this case (attached as Document 9). Do you agree with the way these issues were addressed in this decision?

MEMORANDUM F.

LIST OF MATERIALS PROVIDED TO PARTICIPANTS

On the basis of practical experience, it is suggested that the groups initially be given only the documents specified for their role, together with the Memorandum (G, H, I or J) corresponding to their group. This is intended to encourage independent analysis and diversity of views on the issues raised. The remaining documents could perhaps be made available in the review period.

Doc. No.	TITLE OF DOCUMENT	For Groups
1	European Patent Convention 1973 - selected provisions from Part II Chapter I, Part III Chapter I, Part V and Part VI ('EPC')	A, B, C, D
2	European Patent Application no. 83307553.4 ('the Application')	A, B
3	Haley, J. et. al., "Porcine Relaxin: Molecular Cloning and cDNA Structure", *DNA* 1, 155-162 (1982) ('the *DNA* article')	A
4	European Patent Application publication no. 0,101,309 ('the H1-relaxin patent application')	A, B
5	European Patent Office Examination Report on Application no. 83307553.4 ('the Examination Report')	B
6	"Greens go to law to block human gene patent", *New Scientist,* 1 February 1992, page 16 ('the *New Scientist* article')	C
7	European Patent no. 0,112,149 ('the Patent')	C, D
8	Opposition to European Patent no. 0,112,149 ('the Grounds of Opposition')	D
9	EPO decision on the opposition	After the exercise

MEMORANDUM G.

INSTRUCTIONS FOR GROUP A

EUROPEAN PATENT OFFICE EXAMINATION REPORT

1. Your role

You are an Examiner in the European Patent Office ('EPO'), in the Biotechnology section.

2. Your task

You are to examine European Patent Application no. 83307553.4 ('the Application'), which is Document 2 in the attachments. The Application concerns a gene which encodes for the production in humans of the hormone relaxin. More particularly, you are to examine the Application for compliance with the provisions of the European Patent Convention ('EPC') dealing with Patentability and Filing Requirements –*i.e.* under Part II Chapter I and Part III Chapter I of the EPC (the relevant extracts of which are in Document 1). You are to determine the extent to which the Application satisfies these requirements.

You are provided with two pieces of prior art, found as a result of the Search conducted by the EPO Search Division. These are an article in the scientific journal *DNA* (Document 3) and a published application for another European Patent (Document 4). You are to assume that these two documents are the only relevant documents found as a result of that search.

3. Your questions

- Do all the claims satisfy article 52(1) –*i.e.* are they for an invention that:
- is novel, under articles 54 and 55?
- involves an inventive step, under article 56?
- is capable of industrial application, under article 57?
- Are any of the claims excluded by article 52(2)(a) –*i.e.* are they discoveries?
- Are any of the claims excluded by article 52(4) –*i.e.* are they for methods for treatment of the human body by surgery or therapy?
- Are any of the claims excluded by article 53(a) –*i.e.* are they contrary to "ordre public" or morality?
- Do the claims satisfy article 82 –*i.e.* do they relate only to one invention or inventive concept?
- Do the claims satisfy article 84 –*i.e.* are they clear and concise and supported by the description?

4. Your materials

Document 1: European Patent Convention 1973 - Part II Chapter I, Part III Chapter I, Part V and Part VI (selected provisions)

Document 2: European Patent Application no. 83307553.4

Document 3: Haley, J. et. al., "Porcine Relaxin: Molecular Cloning and cDNA Structure", *DNA* 1, 155-162 (1982)

Document 4: European Patent Application publication no. 0,101,309

MEMORANDUM H.

INSTRUCTIONS FOR GROUP B

PATENT ATTORNEY'S RESPONSE TO EXAMINATION REPORT

1. Your role

You are a European Patent Attorney, specialising in biotechnology patents.

2. Your task

You are to prosecute European Patent Application no. 83307553.4 ('the Application') before the European Patent Office ('EPO'). The Application is Document 2 in the attachments. The Application concerns a gene which encodes for the production in humans of the hormone relaxin.

More particularly, you are to respond to the first substantive Examination Report of the EPO ('the Examination Report'), which is Document 5. This examination considers the extent to which the Application complies with provisions of the European Patent Convention ('EPC') dealing with Patentability and Filing Requirements –*i.e.* under Part II Chapter I and Part III Chapter I of the EPC (Document 1). The Examination Report refers to a published application for another European Patent (Document 4).

3. Your questions

Are the following objections raised in the Examination Report valid:

- the claims lack unity under article 82 –*i.e.* there are three separate inventions, being claims 1-23, claims 24-29 and claims 30-32?
- the claims (inc. claim 1) which refer to "H2-preprorelaxin" per se lack clarity under article 84 –*i.e.* they do not identify the specific structural features which distinguish between H1, H2 and known human relaxin?
- the claims (inc. claim 1) which refer to "or a sub-unit thereof" lack clarity under article 84 and novelty under article 54 –*i.e.* they are not clearly distinguished from certain of the claims in the earlier European Patent Application publication no. 0,101,309 for H1-relaxin?

What amendments, if any, should be made to the Application in light of these objections?

4. Your materials

Document 1: European Patent Convention 1973 - Part II Chapter I, Part III Chapter I, Part V and Part VI (selected provisions)

Document 2: European Patent Application no. 83307553.4

Document 4: European Patent Application publication no. 0,101,309

Document 5: E.P.O. Examination Report on Application no. 83307553.4

MEMORANDUM I.

INSTRUCTIONS FOR GROUP C

OPPONENT'S GROUNDS OF OPPOSITION TO GRANT

1. Your role

You are a member of the European Green Party.

2. Your task

As reported in an article in the *New Scientist* magazine (Document 6 in the attachments), you are to oppose the grant of European Patent no. 0,112,149 ('the Patent') before the European Patent Office ('EPO'). The Patent is Document 7 in the attachments. The Patent concerns a gene which encodes for the production in humans of the hormone relaxin.

More particularly, you are to prepare the Grounds of Opposition, for filing in the EPO. The grounds on which an Opposition may be filed are set out in article 100 of the European Patent Convention ('EPC'), extracts of which are in Document 1.

3. Your questions

Is it feasible to oppose the grant of the Patent on any of the following grounds; that the invention:

- is not capable of industrial application, under article 52(1)?
- is excluded as a discovery, under article 52(2)(a)?
- is excluded as contrary to "ordre public" or morality, under article 53(a)?
- is not novel, under article 54?
- does not involve an inventive step, under article 56?
- If so, what arguments would you make in support of those grounds?

4. Your materials

Document 1: European Patent Convention 1973 - Part II Chapter I, Part III Chapter I, Part V and Part VI (selected provisions)

Document 6: Article in *New Scientist* magazine, 1 February 1992, page 16

Document 7: European Patent no. 0,112,149

MEMORANDUM J.

INSTRUCTIONS FOR GROUP D

PATENT ATTORNEY'S REPLY TO OPPOSITION

1. Your role

You are a European Patent Attorney, specialising in biotechnology patents.

2. Your task

You are to defend an Opposition filed against European Patent no. 0,112,149 ('the Patent') before the European Patent Office ('EPO'). The Patent is Document 7 in the attachments. The Grounds of Opposition are set out in Document 8. The Patent concerns a gene which encodes for the production in humans of the hormone relaxin.

More particularly, you are to prepare the Reply to the Opposition, for filing in the EPO. The grounds on which an Opposition may be filed are set out in article 100 of the European Patent Convention (extracts of which are in Document 1).

3. Your questions

- How should you respond to the technical and legal arguments contained in Parts I and II of the Opposition –*i.e.* the arguments that the invention:
- is excluded as a discovery, under article 52(2)(a)?
- is not novel, under article 54?
- does not involve an inventive step, under article 56?
- How should you respond to the morality arguments contained in Parts III and IV of the Opposition -*i.e.* the arguments that the invention is excluded as contrary to "ordre public" or morality, under article 53(a)?

4. Your materials

Document 1: European Patent Convention 1973 - Part II Chapter I, Part III Chapter I, Part V and Part VI (selected provisions)

Document 7: European Patent no. 0,112,149

Document 8: Opposition to European Patent no. 0,112,149

6.4 Documents for the Relaxin Patent Validity Exercise

1 European Patent Convention 1973 - selected provisions from Part II Chapter I, Part III Chapter I, Part V and Part VI ('EPC')

2 European Patent Application no. 83307553.4 ('the Application')

3 Haley, J. et. al., "Porcine Relaxin: Molecular Cloning and cDNA Structure", *DNA* 1, 155-162 (1982) ('the *DNA* article')

4 European Patent Application publication no. 0,101,309

('the H1-relaxin patent application')

5 European Patent Office Examination Report on Application no. 83307553.4 ('the Examination Report')

6 "Greens go to law to block human gene patent", *New Scientist*, 1 February 1992, page 16 ('the *New Scientist* article')

7 European Patent no. 0,112,149 ('the Patent')

8 Opposition to European Patent no. 0,112,149 ('the Grounds of Opposition')

9 Decision of the EPO on the Opposition

Document 1

Extracts from
THE CONVENTION ON THE GRANT OF EUROPEAN PATENTS (EUROPEAN PATENT CONVENTION) of 5 October 1973

text as amended by the act revising Article 63 EPC of 17 December 1991 and by decisions of the Administrative Council of the European Patent Organisation of 21 December 1978, 13 December 1994, 20 October 1995, 5 December 1996 and 10 December 1998

PART II - SUBSTANTIVE PATENT LAW
CHAPTER I - PATENTABILITY

ARTICLE 52 - PATENTABLE INVENTIONS

(1) European patents shall be granted for any inventions which are susceptible of industrial application, which are new and which involve an inventive step.

(2) The following in particular shall not be regarded as inventions within the meaning of paragraph 1:

(a) discoveries, scientific theories and mathematical methods;

(b) aesthetic creations;

(c) schemes, rules and methods for performing mental acts, playing games or doing business, and programs for computers;

(d) presentations of information.

(3) The provisions of paragraph 2 shall exclude patentability of the subject-matter or activities referred to in that provision only to the extent to which a European patent application or European patent relates to such subject-matter or activities as such.

(4) Methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body shall not be regarded as inventions which are susceptible of industrial application within the meaning of paragraph 1. This provision shall not apply to products, in particular substances or compositions, for use in any of these methods.

ARTICLE 53 - EXCEPTIONS TO PATENTABILITY

European patents shall not be granted in respect of:

(a) inventions the publication or exploitation of which would be contrary to *ordre public* or morality, provided that the exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation in some or all of the Contracting States;

(b) plant or animal varieties or essentially biological processes for the production of plants or animals; this provision does not apply to microbiological processes or the products thereof.

ARTICLE 54 - NOVELTY

(1) An invention shall be considered to be new if it does not form part of the state of the art.

(2) The state of the art shall be held to comprise everything made available to the public by means of a written or oral description, by use, or in any other way, before the date of filing of the European patent application.

(3) Additionally, the content of European patent applications as filed, of which the dates of filing are prior to the date referred to in paragraph 2 and which were published under Article 93 on or after that date, shall be considered as comprised in the state of the art.

(4) Paragraph 3 shall be applied only in so far as a Contracting State designated in respect of the later application, was also designated in respect of the earlier application as published.

(5) The provisions of paragraphs 1 to 4 shall not exclude the patentability of any substance or composition, comprised in the state of the art, for use in a method referred to in Article 52, paragraph 4, provided that its use for any method referred to in that paragraph is not comprised in the state of the art.

ARTICLE 55 - NON-PREJUDICIAL DISCLOSURES

(1) For the application of Article 54 a disclosure of the invention shall not be taken into consideration if it occurred no earlier than six months preceding the filing of the European patent application and if it was due to, or in consequence of:

(a) an evident abuse in relation to the applicant or his legal predecessor, or

(b) the fact that the applicant or his legal predecessor has displayed the invention at an official, or officially recognised, international exhibition falling within the terms of the Convention on international exhibitions signed at Paris on 22 November 1928 and last revised on 30 November 1972.

(2) In the case of paragraph 1(b), paragraph 1 shall apply only if the applicant states, when filing the European patent application, that the invention has been so displayed and files a supporting certificate within the period and under the conditions laid down in the Implementing Regulations.

ARTICLE 56 - INVENTIVE STEP

An invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art. If the state of the art also includes documents within the meaning of Article 54, paragraph 3, these documents are not to be considered in deciding whether there has been an inventive step.

ARTICLE 57 - INDUSTRIAL APPLICATION

An invention shall be considered as susceptible of industrial application if it can be made or used in any kind of industry, including agriculture.

****

PART III - APPLICATION FOR EUROPEAN PATENTS

CHAPTER I - FILING AND REQUIREMENTS OF THE EUROPEAN PATENT APPLICATION

ARTICLE 75 - FILING OF THE EUROPEAN PATENT APPLICATION

(1) A European patent application may be filed:

(a) at the European Patent Office at Munich or its branch at The Hague, or

(b) if the law of a Contracting State so permits, at the central industrial property office or other competent authority of that State. An application filed in this way shall have the same effect as if it had been filed on the same date at the European Patent Office.

****

ARTICLE 78 - REQUIREMENTS OF THE EUROPEAN PATENT APPLICATION

(1) A European patent application shall contain:

(a) a request for the grant of a European patent;

(b) a description of the invention;

(c) one or more claims;

(d) any drawings referred to in the description or the claims;

(e) an abstract

****

ARTICLE 79 - DESIGNATION OF CONTRACTING STATES

(1) The request for the grant of a European patent shall contain the designation of the Contracting State or States in which protection for the invention is desired.

****

ARTICLE 80 - DATE OF FILING

The date of filing of a European patent application shall be the date on which documents filed by the applicant contain:

(a) an indication that a European patent is sought;

(b) the designation of at least one Contracting State;

(c) information identifying the applicant;

(d) a description and one or more claims in one of the languages referred to in Article 14, paragraphs 1 and 2, even though the description and the claims do not comply with the other requirements of this Convention.

ARTICLE 81 - DESIGNATION OF THE INVENTOR

The European patent application shall designate the inventor. If the applicant is not the inventor or is not the sole inventor, the designation shall contain a statement indicating the origin of the right to the European patent.

ARTICLE 82 - UNITY OF INVENTION

The European patent application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept.

ARTICLE 83 - DISCLOSURE OF THE INVENTION

The European patent application must disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

ARTICLE 84 - THE CLAIMS

The claims shall define the matter for which protection is sought. They shall be clear and concise and be supported by the description.

ARTICLE 85 - THE ABSTRACT

The abstract shall merely serve for use as technical information; it may not be taken into account for any other purpose, in particular not for the purpose of interpreting the scope of the protection sought nor for the purpose of applying Article 54, paragraph 3.

****

PART V - OPPOSITION PROCEDURE

ARTICLE 99 - OPPOSITION

(1) Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid.

****

ARTICLE 100 - GROUNDS FOR OPPOSITION

Opposition may only be filed on the grounds that:

(a) the subject-matter of the European patent is not patentable within the terms of Articles 52 to 57;

(b) the European patent does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art;

(c) the subject-matter of the European patent extends beyond the content of the application as filed, or, if the patent was granted on a divisional application or on a new application filed in accordance with Article 61, beyond the content of the earlier application as filed.

ARTICLE 101 - EXAMINATION OF THE OPPOSITION

(1) If the opposition is admissible, the Opposition Division shall examine whether the grounds for opposition laid down in Article 100 prejudice the maintenance of the European patent.

****

ARTICLE 102 - REVOCATION OR MAINTENANCE OF THE EUROPEAN PATENT

(1) If the Opposition Division is of the opinion that the grounds for opposition mentioned in Article 100 prejudice the maintenance of the European patent, it shall revoke the patent.

(2) If the Opposition Division is of the opinion that the grounds for opposition mentioned in Article 100 do not prejudice the maintenance of the patent unamended, it shall reject the opposition.

(3) If the Opposition Division is of the opinion that, taking into consideration the amendments made by the proprietor of the patent during the opposition proceedings, the patent and the invention to which it relates meet the requirements of this Convention, it shall decide to maintain the patent as amended, ……

****

PART VI - APPEALS PROCEDURE

ARTICLE 106 - DECISIONS SUBJECT TO APPEAL

(1) An appeal shall lie from decisions of the Receiving Section, Examining Divisions, Opposition Divisions and the Legal Division. It shall have suspensive effect.

****

ARTICLE 107 - PERSONS ENTITLED TO APPEAL AND TO BE PARTIES TO APPEAL PROCEEDINGS

Any party to proceedings adversely affected by a decision may appeal. Any other parties to the proceedings shall be parties to the appeal proceedings as of right.

****

Module Six - Document Two

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 112 149**
A2

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: 83307553.4

(22) Date of filing: 12.12.83

(51) Int. Cl.³: C 12 N 15/00
C 12 P 21/02, C 07 C 103/52
C 12 N 1/00

(30) Priority: 13.12.82 AU 7247/82

(43) Date of publication of application:
27.06.84 Bulletin 84/26

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

(71) Applicant: HOWARD FLOREY INSTITUTE OF EXPERIMENTAL PHYSIOLOGY AND MEDICINE
c/o University of Melbourne
Parkville Victoria(AU)

(72) Inventor: Hudson, Peter John
1 Sefton Street
Bulleen Victoria(AU)

(72) Inventor: Niall, Hugh David
3 Bendigo Avenue
Elwood Victoria(AU)

(72) Inventor: Tregear, Geoffrey William
62 Hawthorn Grove
Hawthorn Victoria(AU)

(74) Representative: Brown, John David et al,
FORRESTER & BOEHMERT Widenmayerstrasse 4/I
D-8000 München 22(DE)

(54) **Molecular cloning and characterization of a further gene sequence coding for human relaxin.**

(57) Genes and DNA transfer vectors for the expression of human preprorelaxin; sub-units thereof, including genes and transfer vectors for expression of human prorelaxin and the individual A, B and C peptide chains thereof; and equivalents of all such genes. Methods for synthesis of the peptides involving recombinant DNA techniques.

EP 0 112 149 A2

./...

"MOLECULAR CLONING AND CHARACTERIZATION OF A FURTHER GENE SEQUENCE CODING FOR HUMAN RELAXIN"

This invention relates to the molecular cloning and characterization of a gene sequence coding for human relaxin. The invention is also concerned with recombinant DNA techniques for the preparation of human relaxin, prorelaxin and preprorelaxin.

In our Australian Patent Application No. 17906/83 (PF 5352/82, filed 12th August, 1982), we described the molecular cloning and characterization of a gene sequence coding for human relaxin. We have now found a second gene which also codes for human relaxin.

More specifically, this invention relates to an isolated and purified (i.e.,"cloned") human gene coding for prorelaxin, preprorelaxin, and the A and/or B and/or C peptide chains of human relaxin, methods for isolating and purifying the genes and a method for transferring the genes to and replicating the genes in a host cell. The cloned genes are expressed by the host cell when fused with a host-expressable procaryotic or eucaryotic gene. The genes are thus useful in the production of human relaxin for therapeutic purposes.

The invention also relates to the peptides human relaxin, prorelaxin and preprorelaxin, to the individual peptide chains which comprise these sequences and to modified forms of these peptides.

The invention further relates to modified genes coding for the individual relaxin chains and for the above-mentioned modified forms.

[Note: References used in the following description are collected at the end of the description.]

Pioneering work by Hisaw (1926) suggested an important role for the peptide hormone relaxin in mammals through its effects in dilating the pubic symphysis, thus facilitating the birth process. Relaxin is synthesized and stored in the corpora lutea of ovaries during pregnancy and is released into the blood stream prior to parturition. The availability of ovaries has enabled the isolation and amino acid sequence determination of relaxin from pig (James et al, 1977; Schwabe et al, 1977) rat (John et al, 1981) and shark (Schwabe et al, 1982). The biologically active hormone consists of two peptide chains (known as the A and B chains) held together by disulphide bonds, two inter-chain and one intra-chain. The structure thus closely resembles insulin in the disposition of disulphide bonds which has led to speculation of a common ancestral gene for these hormones (James et al, 1977; Schwabe et al, 1977).

Recombinant DNA techniques have been applied to the isolation of cDNA clones for both rat and porcine relaxins (Hudson et al, 1981; Haley et al, 1982), see

also Australian Patent Application No. 11834/83 (PF 2696/82). Synthetic undecamer nucleotides, prepared on the basis of amino acid sequence information, were used as primers for the synthesis of cDNA probes greatly enriched in relaxin cDNA sequences which identified relaxin cDNA clones in libraries derived from both rat and porcine ovarian tissue. The relaxin structural gene was found to code in both cases for a single chain precursor which resembles preproinsulin in the overall configuration, i.e., signal peptide/B chain/C peptide/A chain.

In our Application No. 17906/83 we described the use of probes based on the C peptide region of porcine relaxin to select out a relaxin gene from a human genomic library. This approach resulted in the successful identification of a genomic clone which we have now designated "H1" from which the structure of the entire coding region of a human preprorelaxin was determined.

The present invention arises from a continuation of the work described in Application No. 17906/83 in which we sought to confirm the gene structure described in that application. We have investigated cDNA clones in libraries derived from ovarian tissue from pregnant human females using as a probe a segment of the previously identified human H1 gene corresponding to approximately 300 nucleotides of the C peptide/A-chain coding region (amino acids 64-161). Positive cDNA clones were isolated and sequencing of these revealed a cDNA sequence which was not identical with the sequence previously established and which coded for a form of

preprorelaxin different to that described in our earlier application.

We have also isolated from the human genomic library described in our copending Australian Patent application No. 17906/83 (PF 5352/82) a recombinant phage containing exon 1 of the H2 gene where exon 1 comprises the coding region of the signal, B-peptide, and part of the C-peptide similar to that of the H1-gene.

It is now believed that either or both the presently-described gene which we have designated "H2" and the "H1" gene described in our Application No. 17906/83 are expressed in human reproductive tissue, for example ovary and placenta, and/or other tissues including but not limited to gut, brain and skin, since both genes express peptides with relaxin-like activity.

The corpora lutea of the ovary as well as decidual and placental tissues are the most likely sites for expression of relaxin-related genes. However, in view of the wide distribution of many peptide hormones it is highly likely that the relaxin gene is also expressed in non-reproductive tissues, including brain and the gastrointestinal tract. Relaxin has the general properties of a growth factor and is capable of altering the nature of connective tissue and influencing smooth muscle contraction. We believe that one or both of the gene structures described in this specification and that of Application No. 17906/83 to be widely distributed in the body. We suggest that the relaxin peptides expressed from these genes will play an important

physiological role in addition to their well documented hormonal function during reproduction.

The following abbreviations are used in this description.

H1 - the relaxin gene described in Application No. 17906/83, being deduced from a genomic clone.

H2 - the relaxin gene described herein, being deduced from a cDNA clone.

DNA - deoxyribonucleic acid
RNA - ribonucleic acid
cDNA - complementary DNA (enzymatically synthesized from an mRNA sequence)
mRNA - messenger RNA

A Adenine
T - Thymine
G - Guanine
C - Cytosine
U - Uracil

The coding relationships between nucleotide sequence in DNA and amino acid sequence in protein are collectively known as the genetic code, which is set out below.

First position (5'end)	Second position U	C	A	G	Third position (3' end)
U	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	Stop	Stop	A
	Leu	Ser	Stop	Trp	G
C	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu	Pro	Gln	Arg	G
A	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val	Ala	Glu	Gly	G

The abbreviations used for the amino acids in the table are identified as follows.

Phenylalanine	(Phe)	Histidine	(His)
Leucine	(Leu)	Glutamine	(Gln)
Isoleucine	(Ile)	Asparagine	(Asn)
Methionine	(Met)	Lysine	(Lys)
Valine	(Val)	Aspartic acid	(Asp)
Serine	(Ser)	Glutamic acid	(Glu)
Proline	(Pro)	Cysteine	(Cys)
Threonine	(Thr)	Tryptophan	(Try)
Alanine	(Ala)	Arginine	(Arg)
Tyrosine	(Tyr)	Glycine	(Gly)

Each 3-letter codon represented in the table, e.g., AUG, CAU (otherwise known as a deoxynucleotide triplet or nucleotide triplet) corresponds to a trinucleotide of mRNA, having a 5'-end on the left and a 3'-end on the right. The letters stand for the purine or pyrimidine bases forming the nucleotide sequence. All DNA sequences given herein are those of the strand whose sequence corresponds to the mRNA sequence, with thymine (T) substituted for uracil (U).

The invention will be further described and elucidated in the following discussion. Reference will be made to the accompanying drawings in which:

Figure 1 : shows an abbreviated restriction map and sequencing strategy for the cDNA clone in pBR322, genomic clone H11, and GT10 cDNA clones a-f. Arrows indicate the direction of sequencing on end-labelled fragments (see methods). GT10 clones a-f were sequenced by subcloning into an M13 vector as described hereinafter. Nucleotides are numbered from the AUG initiation codon, position 1-3, to the termination codon, position 554-556.

Figure 2 : compares the amino acid and mRNA sequence of human preprorelaxin H2 (upper) with the corresponding H1 (lower) sequence. The sequences have been aligned to maximize homology with nucleotide identities being indicated by asterisks and amino acid homologues by boxed-in areas. Amino acids are numbered from the start of the B-chain (H2 gene sequence starting at -1 and H1 sequence at +1) although this position represents only the hypothetical start of the B chain sequence and has been deduced simply from the homology

to the related porcine and rat preprorelaxin structures. The asterisk beneath Ala 45 in the C peptide denotes the position of an intron in the G/CA codon in both genes.

Figure 3: autoradiographs of identical nitrocellulose strips taken from either a) Northern gel transfer of human ovarian RNA or b) λplaques corresponding to the H1 gene (λH7) or H2 gene (λGT10-a) using as hybridization probes A: a random primed 600 bp H2 relaxin cDNA fragment (72-660), B: H2-specific 25 mer (483-507), C: H1-specific 25 mer (483-507), D: H1-specific 25 mer (248-272).

Figure 4 : autoradiographs of identical nitrocellulose strips following Northern gel transfer of human ovarian RNA using as hybridization probes fragments of the H2 cDNA clone in pBR322 (see Figure 1).

A: 600 bp fragment (72-660) corresponding to most of the coding region

B: 5' untranslated region (to Hinf I site at nucleotide 30)

C: 3' untranslated region (from Hinf I site at nucleotide 660)

D: 3' untranslated region (from Hpa I site at nucleotide 850)

Figure 5: comparison of the amino acid sequences of the B and A chains between the two human relaxin genes, human insulin, and other members of the relaxin family. Boxed areas highlight residue which are conserved between the two human relaxin genes and the relaxin family. Arrows indicate probable sites of proteolytic cleavage with confirmation by protein sequencing data of the amino terminal residue of the B and A chains of

porcine (Schwabe et al, 1977; James et al, 1977), rat (John et al, 1981), shark (Schwabe et al, 1982) and dogfish relaxins (Schwabe et al, 1983).

The H2 mRNA sequence shown in Figure 2 was determined by the methods described hereinafter. For ease of comparison, the numbering of the amino acids previously used for the peptide derived from the H1 sequence has been maintained in the present description of the H2-derived peptide. The structure of H1-preprorelaxin was deduced from the genomic sequence by comparison with the homologous structures of pig and rat relaxin. The H2-preprorelaxin structure was deduced by comparison with the H1 structure as well as the pig and rat structures. Confirmation of the A and B peptide chain structures has been provided by synthesis and chain recombination in vitro which produces a material which is biologically active in the uterine contraction assay.

It will be seen from Figure 2 that the present and previous sequences show significant differences as well as similarities. Notable are:

(1) Significant amino acid differences in three main areas:
    (a) the N-terminus of the B-chain
    (b) the N-terminus of the A-chain
    (c) the middle of the C-peptide.

(2) Regions of strong homology in the B-chain and C-peptide:

(a) 120 identical bases from Val^{6} to Ile^{47}.

(b) 88 - 90 identical bases from Phe^{101} to Ser^{132}.

The two genes are therefore very similar but the differences are sufficient to indicate that the H2- gene is indeed a second gene and not simply a polymorph of H1.

The mode of in vitro processing of the H1 preprorelaxin is not yet fully known but by analogy with pig relaxin, cleavage of the signal peptide would be expected to occur at the Ala^{-1}-Lys^{1} bond. Similarly excision of the H1-C peptide is predicted to occur at Leu^{32} - Ser^{33} and Arg^{136} - Arg^{137}, thus giving the H1-B and H1-A chains of respectively 32 and 24 residues (Figure 2).

In H2 preprorelaxin Ala^{-1} has been replaced by Asp and so we would predict cleavage of the signal peptide after the alanine corresponding to position -2 in H1. Cleavage at the H2-B chain/C peptide junction is expected after Leu^{32} by anlogy to all other prorelaxins, thus leaving the H2-B chain with 33 residues. Cleavage at the H2-C peptide/A chain junction would occur after Arg^{136} by analogy to rat preprorelaxin, thus leaving the H2-A chain with 24 residues.

As noted in our studies on pig relaxin, there are core sequences in the pig relaxin B and A chains which contain all the essential elements for biological activity. Our synthetic studies on the human relaxin

chain show similar results, as set out in more detail hereinafter.

According to one aspect of the present invention, there is provided a gene for the expression of human H2-preprorelaxin.

Except where otherwise specified, all following references to the gene sequences for preprorelaxin, prorelaxin, relaxin and the signal, A, B and C peptides, and to the peptides themselves will be understood to refer to the H2 varients and to exclude the H1 variants.

More specifically, this aspect of the invention provides a double-stranded DNA fragment for the expression of human preprorelaxin, which comprises a coding strand and a complementary strand corresponding to the complete mRNA (codons -25 to 160) sequence shown in Figure 2 of the accompanying drawings.

The invention also includes any sub-unit of the H2-preprorelaxin gene sequence described herein, or any equivalent of the said sequence or sub-unit. Among the sub-units to be included by this statement are the individual structural genes coding for the signal peptide chain and the separate H2-A and H2-B peptides and the H2-C chain of human preprorelaxin (see Figure 2) and any combinations of these chains, e.g., the genes for expressing the H2-A and H2-B peptides, separately or as prorelaxin (with the H2-C chain). The sub-units also include fragments and combinations of fragments of any of said gene sequences.

Thus according to another aspect of the present invention, there is provided a gene for the expression of human prorelaxin.

More specifically, this aspect of the invention provides a double-stranded DNA fragment for the expression of human prorelaxin, which comprises a coding strand and a complementary strand corresponding to the codons numbered as 1 to 160 of the mRNA sequence shown in Figure 2 of the accompanying drawings.

According to a further aspect of the present invention, there are provided genes for the separate expression of the A, B and C chains of human relaxin or any combination of two or more of the said chains and any fragment or combination of fragments of the said chains.

More specifically, this aspect of the invention provides double-stranded DNA fragments for the separate expression of the A and/or B and/or C chains of human relaxin (or fragments as described above) which comprise a coding strand and a complementary strand corresponding to the codons numbered -1 to 32, 33 to 136 and 137 to 160 of the mRNA sequence shown in Figure 2 of the accompanying drawings.

The genes described above in addition to the codons specified may also include the appropriate "start" and "stop" codons, e.g., AUG and UGA respectively (codons -25 and 161 in Figure 2).

Those skilled in the art will appreciate that polymorphic forms of the genes may exist. Such forms are included in the present invention.

The invention further includes the complements of the above sequences, sub-units or equivalents, and the corresponding RNA sequences, sub-units or equivalents.

According to another aspect of the present invention there is provided a DNA transfer vector comprising the deoxynucleotide sequences corresponding to the genes defined above.

As shown above, the genetic code contains redundancies, that is certain amino acids are coded for by more than one codon. Thus the invention includes deoxynucleotide sequences in which the codons depicted in the drawings, or their cDNA equivalents are replaced by other codons which code for the same amino-acid.

Furthermore, as already indicated above, peptides with relaxin activity may be produced which differ from the B and/or A chain structures of natural relaxin. Such differences may involve deletion of one or more amino acids and/or addition of further amino acids and/or substitution of different amino acids in the natural chains.

Thus the invention also includes genes and DNA transfer vectors as described above wherein one or more of the natural codons are deleted and/or are replaced by codons which code for amino acids other than that coded by the natural codon, and/or further codons are added to the natural sequence.

The transfer vectors of the invention may also include inter alia, genetic information which ensures their replication when transferred to a host cell. Such cells may include, for example, the cells of procaryotic microorganisms, such as bacteria, yeasts and moulds, and also eucaryotic cells, including mammalian cells and cell lines.

Examples of transfer vectors commonly used in bacterial genetics are plasmids and the DNA of certain bacteriophages. Both phage DNA and bacterial plasmids have been used as the transfer vectors in the present work. It will be understood however, that other types of transfer vectors may be employed. The general techniques of forming such transfer vectors and transforming them into microorganisms are well known in the art.

The invention also includes a procaryotic or eucaryotic cell transformed by any of the transfer vectors described above.

One preferred microorganism is the very familiar Escherichia coli, but any other suitable microorganism may be used.

According to a still further aspect of the present invention, there is provided a process for making a DNA transfer vector for use in maintaining and replicating a deoxynucleotide sequence coding for human preprorelaxin, characterised by ligating a deoxynucleotide sequence coding for human preprorelaxin with a DNA molcule prepared by cleaving a transfer vector with a restriction enzyme.

DNA transfer vectors for use in maintaining and replicating deoxynucleotide sequences coding for human prorelaxin and for the A and B chains of human relaxin may be similarly prepared from the appropriate deoxynucleotides.

The A and B peptide chains, and also prorelaxin and preprorelaxin may be prepared by the usual process of gene expression, that is by growing cells containing the appropriate transformed transfer vector and isolating and purifying the required peptide(s) produced by the cells.

Thus, the invention further includes a process for making a fusion protein comprising the amino acid sequence of human preprorelaxin as its C-terminal sequence and a portion of a procaryotic or eucaryotic protein as its N-terminal sequence, characterised by incubating a cell culture transformed by an expression transfer vector comprising a deoxynucleotide sequence coding for human preprorelaxin, prepared in accordance with the process described above.

Fusion proteins comprising the amino acid sequences for human prorelaxin and/or the A and/or B and/or C chains of human relaxin may be similarly prepared.

The fusion peptide products thus produced will be in the form of a fusion protein in which the desired peptide is linked with a portion of a procaryotic or eucaryotic protein characteristic of the host cell. Such fusion proteins also form a part of this invention.

The invention also includes a process for synthesizing human prorelaxin comprising the A and B peptides separated from each other by a C peptide, characterised by incubating a culture of cells, transformed by an expression transfer vector comprising a deoxynucleotide sequence coding for said human prorelaxin, prepared as described above, under conditions suitable for expression of said sequence coding for human prorelaxin, and purifying human prorelaxin from the lysate or culture medium of said cells.

The peptide of interest can be recovered from the fusion product by any suitable known cleavage procedure.

As already indicated above the transfer vector may be modified by codon substitution /deletion/addition and such modifications will give rise to modified fusion peptides. In this way appropriate modifications may be made to facilitate the cleavage of the fusion peptides, for example, at the junction of B/C or C/A chains or to modify the peptide chain behaviour during subsequent chemical or biological processing.

As indicated above, the invention also provides human relaxin, prorelaxin and preprorelaxin.

Relaxin may be prepared by direct combination of the separate A and B chains by any of the procedures currently known and used for the preparation of insulin.

Also in a similar manner to insulin, relaxin may be prepared from prorelaxin by oxidizing or otherwise converting the sulfhydryl groups on the A and B peptides

of relaxin, prepared as described herein, to form disulfide crosslinks between said A and B peptides, and then excising the C peptides, for example, by an enzyme-catalyzed hydrolysis specific for the bonds joining the C peptide to the A and B peptides.

Accordingly, the present invention further provides a method for the synthesis of human relaxin which comprises combining the A and B chains of relaxin (in their full-length, shortened or modified forms) by methods known per se for combination of A and B chains of human insulin.

One such method comprises reducing a mixture of the S-sulphonated A and B chains and then allowing the mixture to oxidize in air.

We have also found that the efficiency of the above procedure is improved when one or both of the A and B chains is in the form of an S-thioethyl-cys derivative rather than the S-sulpho form.

In our Australian Patent Application No. 15413/83 (PF 4385/82) we also showed that one or both of the A and B chains of relaxin can be shortened at the amino and/or carboxy terminii without significant loss of biological activity and with improved combination yields. These techniques apply equally to the preparation of human relaxin.

Another aspect of the invention provides a human relaxin analogue consisting essentially of shortened and/or modified forms of the natural B and/or A peptide chains.

This aspect of the invention also provides a method for producing a human relaxin analogue which comprises the step of forming the shortened and/or modified B and/or A peptide chains and combining them by any of the methods described above.

Our investigations with both pig and human relaxin (H1) show that relaxin activity may be present with human A chains as short as A(10-24) and B chains as short as B(10-22) although the expected practical minima are respectively A(4-24) and B(4-23). The peptide A(4-24)-B(1-25) is already known to have relaxin activity.

In general, for the present relaxin structure (H2) the A chain can be varied from A(1-24) to A(10-24) and B chain from B(-1-32) to B(10-22).

The preferred combinations are derived from:

A		B
(1-24)		(-1-23)
any of (2-24)	with any of	(up to)
(3-24)		(-1-31)

Modifications of the B and/or A chains, in accordance with the present invention may involve either "genetic" modification, as described above, or chemical modification of the B and/or A chains (in either full-length or shortened form) prior to combination by the method of the invention. Two types of modification may be employed, either singly or in combination.

The first type involves the modification of one or more of the amino-acids which occur in the natural or shortened B and/or A chains. Such modification will generally involve protection of active groups on one or more of the amino-acids by methods known per se, and the protecting groups may, if desired, be removed after combination of the (modified) A and B chains.

Examples of this type of modification include the acetylation, formylation or similar protection of free amino groups, including the N-terminal, amidation of C-terminal groups, or the formation of esters of hydroxyl or carboxylic groups. The formyl group is a typical example of a readily-removable protecting group.

The second type of modification includes replacement of one or more of the natural amino-acids in the B and/or A chains with a different amino acid (including the D-form of a natural amino-acid). This general type of modification may also involve the deletion of a natural amino-acid from the chain or the addition of one or more extra amino-acids to the chain.

The purpose of such modifications is to enhance the combination yields of the A and B chains, while maintaining the activity of the product, i.e., relaxin or an analogue thereof, or to enhance or modify the activity of the product for a given combination yield. Such modification may extend to the production of synthetic analogues which have relaxin-blocking or -antagonistic efrects.

A specific example of the first type of modification is the modification of the tryptophan (Trp) residue at B2 by addition of a formyl group.

Examples of the second type of modification are replacement of the Met moiety at B24 with norleucine (Nle), valine (Val), alanine (Ala), glycine (Gly), serine (Ser) or homoserine (HomoSer).

The invention in this aspect also includes human relaxin analogues formed from natural or shortened B and/or A chains modified in accordance with the invention as described above.

The A and B peptide chains, and also prorelaxin and preprorelaxin may be prepared by the usual process of gene expression, that is by growing a microorganism containing the appropriate transformed transfer vector and isolating and purifying the required peptide(s) produced by the microorganism.

The peptide products thus produced may be in the form of a fusion protein in which the desired peptide is linked with a portion of a procaryotic protein

The invention is further described and illustrated by the following description of the experimental procedures used and the results obtained thereby.

Methods and Materials

Messenger RNA isolation and cDNA cloning

Human ovarian tissue obtained during surgery for the treatment of an ectopic pregnancy was quickly frozen on dry ice and the RNA isolated in 5M guanidinium thiocyanate (Merck) according to the method of Chirgwin et al., 1979. Poly-A^+ RNA was converted into double stranded DNA (Wickers et al, 1978) and cloned either by the homopolymeric G/C tailing method into a pBR322 plasmid vector (Chang et al., 1978) or by the lambda packaging method using the λGT10 vector (Huynh et al., 1983). In our experience the efficiency of transformation with the pBR322 method (10^4 recombinants/µg of cDNA) was far less efficient than the lambda technique (up to 10^6 recombinants/µg of cDNA).

Preparation of hybridization probes

Radiolabelled probes were prepared by primed synthesis on various DNA fragments using denatured random primers of calf thymus DNA (Hudson et al., 1983, Taylor et al., 1976). The DNA template (100-200 ng) was denatured with the random primers (1 µg) by boiling in 20 µl of water for 2 minutes. Synthesis was initiated by the addition of a 30 µl reaction mixture containing 50mM Tris-HCl pH 8.0, 50mM NaCl, 1mM DTT, 10mM $MgCl_2$, 5 units of E. coli DNA Polymerase 1 (Klenow fragment), 500 µM each of dCTP, dGTP, dTTP and 0.3 µM α-[^{32}P]-dATP (Approx. 3000 Ci/mmol, Amersham). After incubation at 37°C for 30 minutes the reaction was terminated by dilution into 300 µl of a buffer containing 0.3M NaCl, 10mM Tris-HCl, pH 8.0, 1mM EDTA

and passed through a Sephadex-G50 column, (1cm x 5cm) in the same buffer. The radiolabelled probe was collected from the peak fractions at void volume and precipitated with 2 volumes of ethanol at -20°C for 2 hours using tRNA (10 µg) as carrier.

Selection of specific cDNA clones

To screen the human ovarian cDNA clone bank for relaxin specific sequences we used as a probe a segment of the previously identified human H1 gene corresponding to a 400 nucleotide segment coding for the C peptide and A-chain from amino acid 64, through the termination codon and including 80 bases of the 3' untranslated region. A single positive cDNA clone from the pBR322 library was isolated and sequenced. 23 unique recombinants were isolated from the λGT10 libraries, but of these only 6 were subjected to complete nucleotide sequence analysis.

DNA sequence analysis

The sequencing strategy and an abbreviated restriction map of the cDNA clones are summarized in Figure 1. The recombinant plasmid in pBR322 was digested with restriction enzymes Hpa II (P), Hinf I (F) or Taq I (T) and end-labelled using reverse transcriptase and the appropriate α-labelled deoxynucleotide triphosphate (dCTP for Hpa II, and Taq I, dATP for Hinf I). Fragments were cleaved internally with a second restriction endonuclease and then separated by electrophoresis on 8% polyacrylamide gels prior to sequencing by the chemical degradation method of Maxam and Gilbert et al, 1977.

cDNA clones in λGT10 were sequenced by subcloning Eco R1 restriction fragments into M13mp9 and employing the techniques described by Sanger et al, (1977).

Southern and Northern gel analyses

Performed on purified genomic DNA after restriction endonuclease cleavage by the method of Southern (1975) or on purified RNA. The DNA fragments which were used as probes were found to be specific for either exon I or exon II of the H1 genomic clone despite having a small amount of flanking sequences. These fragments were generated by subcloning into M13mp8 a 500 bp Alu I fragment of the λH7 clone in the case of the exon I probe, or a 400bp Eco RI-Ava II fragment for the exon II probe. A probe from the H2 cDNA clone was generated by digesting with Hinf I and isolating a 300 bp doublet corresponding to the coding region from Asp 1 to the termination codon and including 110 bases of the 3' untranslated region (Figure 1). Oligonucleotide probes were synthesized by the phosphite chemistry method of Beaucage and Caruthers (1981) and were end-labelled with γ-^{32}P-ATP using T4 polynucleotide kinase. Hybridization conditions were calculated on the basis of the G+C content.

Isolation and nucleotide sequence analysis of the H2 genomic clone

The human genomic lambda library of Lawn et al (1978) was screened by method described earlier (Hudson et al, 1983) except that a mixture of DNA fragments corresponding to exons I and II of the H1 genomic clone

was used for the probe as described above. Positive phage were grown in litre scale liquid cultures, the DNA isolated and digested with restriction endonucleases prior to mapping with the exon I and II probes. A 4 kilobase EcoR1 fragment was found to contain the entire exon I coding region which differentiated this clone from the homologous H1 gene structure. This fragment was subcloned into M13mp8 and sequenced by the technique of Maxam and Gilbert (1977). After digesting with Ava I, fragments spanning the coding region were end-labelled and cleaved internally by a second restriction enzyme (Hpa II of Hinf I) to generate fragments suitable for sequence analysis.

Isolation of a cDNA clone

Samples of human corpus luteum were made available to us as a result of surgical intervention in ectopic pregnancies or from lutectomy at the time of Caesarian section. From the RNA isolated from a single corpus luteum a cDNA library was constructed in pBR322 providing about 300 unique recombinants. Screening this library with an H1-cDNA probe revealed a single recombinant with sequence homology to human relaxin I. To increase the total number of recombinants from such small amounts of ovarian tissue we constructed cDNA libraries using the λGT10 cloning system (Huynh et al, 1983). Screening with a relaxin-specific probe identified 23 unique cDNA clones of which six were characterized as shown in Figure 1. Nucleotide sequence analysis revealed that all 6 cDNA recombinants encoded fragments of the same relaxin structural gene (Figure 2), yet this sequence was different to the genomic clone reported earlier (Hudson et al., 1983).

We expected that this novel sequence corresponded to the second human relaxin gene (H2) which had been observed in genomic DNA.

Surprisingly, none of the cDNA clones contained a polyadenosine sequence at the 3' end, although the size of cDNA clones in PBR322 and λGT10 (1800 bp and 1900 bp respectively) indicate that large transcription products were being synthesized during the cloning procedure. These two cDNA clones had overlapping sequence identity at the 3' terminus confirming that they were derived from the same mRNA structure. We attributed the loss of the poly-A tail either to premature termination of the double-stranding transcription reaction or to excessive S1 nuclease degradation during the cloning procedure.

Isolation of a genomic clone corresponding to the second gene

A thorough screen of 10^8 recombinant phage from the human genomic library of Lawn et. al., (1978) using mixed probes specific for exon I or II of the λH7 relaxin clone revealed 16 positive phage. Small scale restriction mapping analysis revealed that 14 of these recombinant phage corresponded to the H1 relaxin gene reported earlier (11 were identical to the λH7 genomic clone; 3 were identical to λH5 a different genomic clone of the H1 gene as previously reported by Hudson et. al., 1983). However, the other 2 recombinant phage were identical and had a unique restriction pattern characteristic of the H2 relaxin gene whose structure is given in Figure 1. The unusual ratio of recombinants reflects either their proportion in the

original genomic library or results from selective growth during amplification. Southern blot analyses of this new recombinant phage (λH11) using separate probes corresponding to either exon I or II of the λH7 clone, revealed that λH11 contained only the exon I coding region. Attempts to find a full length genomic clone corresponding to the H2 relaxin gene either in the library of Lawn et. al. (1978) or in another library (Dr. R. Crawford, unpublished) have so far been unsuccessful.

The nucleotide sequence of the relaxin coding region of λH11 was found to be identical to that observed in the cDNA clone shown in Figure 2. An intron interrupts the coding region in exactly the same position as in the λH7 genomic clone (Hudson et. al., 1983) suggesting that these genes arose by a gene duplication event at some point in evolution.

Northern gel analysis

RNA was isolated from several samples of human corpora lutea taken from different individuals during surgical intervention for ectopic pregnancy or during Caesarian section operations. Northern gel analysis using probes made from the coding region of either relaxin gene revealed that two major mRNA species of approximate sizes 1000 bp and 2000 bp were present in five human ovarian RNA samples tested (Figure 3). The smaller mRNA species were 2-3 fold more abundant in the RNA samples tested and this result was independent of whether the probe used in the analysis corresponded to H1 or H2 relaxin indicating that high cross-hydridization rates occur under our experimental conditions. To differentiate whether these two mRNA

species represent the separate products of the H1 and H2 genes, oligonucleotide probes were synthesized over a region of minimum homology (60%) between the two relaxin genes (residues 137-144 in Figure 2). These synthetic 25 mers were radiolabelled by kinasing with γ-^{32}P-ATP and used as hybridization probes under conditions shown to provide specificity for either the H1 or H2 gene (Figure 3). Northern gel analysis using these radiolabelled probes revealed that both mRNA species corresponded to products of the H2 gene. We could not detect any transcription products from the H1 gene using the specific probes, although low level expression (less than 5% of the H2 level) would have been difficult to identify.

To analyse the different mRNA transcripts from the H2 gene, we made specific probes from segments of the two large H2 cDNA clones corresponding to the coding region and 5' and 3' untranslated regions (Figure 4). The larger mRNA transcript (approximately 2kb in length) selectively hybridized to segments of the 3' untranslated region from both cDNA clones, from a position approximately 100 bases from the termination codon. A potential polyadenylation signal exists in the nucleotide sequence of the cDNA clones, 140 bases from the termination codon, and this region does have homology to the porcine relaxin polyadenylation site. However, the question of whether the shorter mRNA product is polyadenylated near this position cannot be resolved until full length cDNA clones corresponding to both mRNA forms have been isolated and characterised.

In the absence of the genomic sequence of the H2 gene it is impossible to define the mechanisms leading

to the formation of the two mRNA transcripts. It is possible, like the collagen and β-microglobulin genes, that cleavage of the primary RNA transcript could occur at alternative polyadenylation sites. On the other hand we cannot rule out the possibility of alternative splicing mechanisms such as occurs in the calcitonin, growth hormone and α-crystallin genes.

The primary structure of preprorelaxin encoded by the H2 gene

The mode of in vivo processing of the human preprorelaxin genes is not yet fully understood and has to be deduced by analogy to the processing of porcine and rat preprorelaxins (Figure 5). The predicted B and A chain structures for the H1 and H2 genes have been aligned to other members of the relaxin family and human insulin in Figure 5.

Cleavage of the signal peptide in H1 has been predicted (Hudson et al., 1983) to occur after a short side chain residue such as Ala^{-1}, -2 or -4 or after Ser-6. Cleavage after Ala-1 is consistent with the homology to porcine preprorelaxin and human preproinsulin. Similarly, cleavage of the H2 signal peptide probably occurs after Ala-2 by such analogy, although cleavage after Ala-4 or Ser-6 are other possibilities.

By analogy to rat and pig prorelaxins, cleavage at the B chain/C peptide junction would occur after Leu 32 in both H1 and H2 precursors. However, both human relaxin B chains possess at positions 29-30 the conserved dibasic sequence Lys-Arg, which is a known

processing site in other prohormones such as proinsulin, and cleavage here cannot be excluded. Direct amino acid sequence analysis of relaxin isolated from corpora lutea of pregnancy will be required to settle this point. In the meantime it seems that the most likely structure of the H1 B chain would be 32 residues in length (Lys 1 to Leu 32) and the H2 B chain would be 33 residues (Asp-1 to Leu 32).

Cleavage at the C peptide/A chain junction of H1 prorelaxin has been predicted (Hudson et al., 1983) to occur after Arg 136 within a group of 4 basic residues because the Arg-Pro imide bond at 137-138 would be resistant to proteolysis. H2 prorelaxin has the same sequence of 4 basic residues and a similar processing step after Arg 136 would result in both the H1 and H2 relaxin A chains being 24 residues in length.

Biological Activity of the H2 gene

As noted in earlier studies on synthetic pig relaxin peptides, there are core sequences in the pig relaxin B and A chains which contain all the essential elements for biological activity. Our synthetic studies on the H1 relaxin peptides has shown that combination of the complete H1 A chain (Arg 137-CYS 160) to a shortened form the H1 B chain (Lys 1-Ser 25) produced material which possessed biological activity (Hudson et al., 1983). Further studies on both the H1 and H2 gene structures using peptide synthesis reveals that both genes code for forms of relaxin which are biologically active in the rat uterine contractility assay.

Chemical Synthesis of a modified human relaxin H2 (hRLX) A(1-24) - B(-1-24)

(i) Synthesis of human relaxin A-chain, H2 hRLX A(1-24)

The amino acid sequence corresponding to residues 1 to 24 of the human relaxin A-chain, deduced as described above from the nucleotide sequence of the cDNA clone, was synthesized by the solid-phase procedure according to the general principles described by Merrifield (e.g. Barany, G. and Merrifield, R.B. In "The Peptides". Ed. E. Gross & J. Meienhofer, Academic Press, N.Y., pp. 1-284, 1980).

N-α-tertiarybutyloxycarbonyl*-4-methyl-benzyl-L-cysteine (*hereinafter "BOC") was coupled to a 1% crosslinked polystyrene resin via the phenylacetamidomethyl (PAM) linkage to a level of 0.30 mmole/gm using the method of Tam et al., (Synthesis 12, 955-957, 1979). The BOC-L-CYS-PAM resin (8.0 gm) was transferred to the reaction vessel of a Beckman Model 990 Peptide Synthesizer and the amino acid sequence from residues 23 through to 1 was assembled by the stepwise addition of each suitably protected amino acid. The amino terminal BOC protecting group of each amino acid was removed by treatment of the resin with 35% trifluoroacetic acid in methylene chloride for 30 minutes followed by neutralization with 5% diisopropylethylamine in methylene chloride for 15 minutes. After each treatment the resin was washed thoroughly with methylene chloride. The next amino acid in the sequence (suitably protected at the α-amino

with the BOC group and where necessary with the 7side-chain functional group appropriately protected) was coupled to the resin using dicyclohexylcarbodiimide (DCC). The resin was stirred with the amino acid in methylene chloride for 10 minutes prior to the introduction of the DCC which was also dissolved in methylene chloride. A 2.5 molar excess (6.0 mmole) of amino acid and DCC was used for each coupling. After stirring for 1 hour a sample of the resin was removed from the reaction mixture and tested for the presence of free amino groups using the ninhydrin procedure of Kaiser et al.

(Anal. Biochem., 34, 595-598, 1970). If the ninhydrin test was negative indicating complete coupling the reaction cycle was continued with BOC deprotection, neutralization and coupling of the next amino acid. For a positive ninhydrin test the coupling reaction was repeated with further amino acid and DCC.

Amino acids with side-chain functional groups were used as the following protected derivatives: N-α-BOC-2,6-dichlorobenzyl-L-tyrosine, N-α-BOC-ε-chlorobenzyloxycarbonyl-L-lysine; N-α-BOC-L-serine O-benzyl ether; N-α-amyloxycarbonyl - N^G-tosyl-L-arginine; N-α-BOC-L-threonine O-benzyl ether; N-α-BOC-S-ethyl mercapto-L-cysteine (for CYS at A-chain sequence position 15, 11 and 10).

Following the assembly of the 1-24 peptide sequence, the final BOC group on the amino terminal arginine was removed using the deprotectdion neutralization cycle and the peptide-resin dried in vacuo (wt of peptide resin 13.0 gm). A portion of the

peptide-resin (2 gm) was treated with anhydrous hydrogen fluoride in the presence of anisole (2 ml) at 0°C for 30 minutes. The total time for contact of the resin-peptide with hydrogen fluoride (HF) was kept to a minimum (not more than 70 minutes) by rapid removal of the HF under oil-pump vacuum. The resin-peptide was then washed several times with ethyl acetate to remove excess anisole, the peptide extracted into 1M acetic acid and the solution lyophilized. The yield of crude peptide, (with the cysteines at positions 10, 11 and 15 still protected as the S-thioethyl derivative) was 392 mg. Initial purification of the crude peptide was by gel-filtration on Biogel P10 in 0.1M acetic acid. The fractions representing the major peak from this column, which eluted at a position corresponding to a molecular weight of approximately 3000, were collected and lyophilized. Amino acid analysis of a sample of this peptide indicated that all the amino acids of the 1-24 sequence were present in the correct ratio.

Further purification of the [S-thioethyl $Cys^{10,11,15}$]-hRLX A(1-24) peptide was effected by preparative reverse-phase HPLC on a Waters C-18 Bondapak column using a 0.1% TFA-water/acetonitrile solvent system.

A sample (80 mg) of the peptide purified by gel-filtration was S-sulfonated with a mixture of sodium sulfite and sodium tetrathionate (total reaction time of 3 hours) according to the method described by Du et al., (Scientia Sinica, 10I, 84-104 (1961)). The precipitate which formed during the S-sulfonation reaction was removed by filtration and both the precipitate and the supernatant solution dialyzed

against distilled water at 4°C for 48 hours. The contents of the dialysis bags were lyophilized to yield 39.5 mg of peptide from the supernatant solution and 20.3 mg of peptide from the precipitate which occurred during the S-sulfonation reaction. A sample of the 'soluble' [S-sulfo $Cys^{10,11,15,24}$] hRLX A(1-24) peptide was purified by preparative reverse-phase HPLC on a Waters C-18 Bondapak column using a 0.1% TFA-water/acetonitrile solvent system.

(ii) Synthesis of shortened human relaxin B-chain, H2 hRLX B(-1-24)

The amino acid sequence corresponding to residues -1 to 24 of the H2 human relaxin B-chain was synthesized using the procedures described above and commencing with 6.0 gm N-α-tertiarybutyloxycarbonyl-L-methionine-O-benzyl-L-serine-phenylacetamido-methyl polystyrene resin with a loading of 0.5 mmole Met per gm. The side-chain protecting groups used in the A-chain synthesis were also employed for the B-chain including the S-ethyl mercapto derivative for both cysteines at positions 10 and 22. The glutamic acid residues at positions 4 and 5 and the aspartic acid residue at -1 were added as the N-α-BOC-benzyl ester derivative. The glutamine at position 18 was coupled by the active ester procedure using N-α-BOC-L-glutamine-p-nitrophenyl ester in DMF. Following coupling of the tryptophan at position 2, 0.1% indole was added to the trifluoroacetic acid deprotecting reagent and to the subsequent methylene chloride washes.

The final weight of peptide-resin after removal of the BOC group from the amino terminal aspartic acid

residue and vacuum-drying was 8.5 gm. A portion of the peptide resin (3.5 gm) was treated with anhydrous hydrogen fluoride in the presence of anisole (2 ml) at 0°C for 30 minutes and the B-chain peptide isolated using the procedure described above for the A-chain. The crude [S-thioethyl $Cys^{10,22}$] hRLX B(-1-24) (0.97 gm) was purified by gel filtration on BioGel P10 in 1M acetic acid followed by preparative HPLC.

A sample (100 mg) of the peptide purified by gel filtration was S-sulfonated at pH 8.3 for 3 hours, the reaction mixture filtered and the precipitate and supernatant solutions dialyzed against distilled water. The 'soluble' peptide recovered after lyophilization was 42.4 mg; the 'insoluble' peptide was 59.5 mg. The S-sulfonated B-chain peptides were further purified by preparative HPLC using a C-18 reverse-phase column and 0.1% TFA-water-acetonitrile solvent system.

(iii) Chain Combination

The synthetic H2 hRLX A(1-24) and H2 hRLX B(-1-24) peptides were combined using the procedure described by Chance and Hoffmann (Australian Patent Application No. 68844/81) for insulin chains wherein the S-sulfonated peptides were mixed in a ratio of A : B of 2.6: 1 at a peptide concentration of 10 mg/ml in glycine buffer pH 10.5. Dithiothreitol in glycine buffer was then added in an amount to give a total of 1.0 sulfhydryl groups for each S-sulfo group. The reaction mixture was then stirred in an open vessel for 24 hours.

As a further modification to this procedure we have found that the chain combination reaction to form

biologically active relaxin proceeded efficiently when one or preferably both of the peptide chains are used as their S-thioethyl-Cys derivatives rather than in the S-sulfo form specified by Chance and Hoffmann (op.cit.) in the case of insulin. The use of S-thioethyl Cys peptides eliminates a reaction and purification step required to convert the peptides to the S-sulfo derivatives. In our experience the S-sulfonation reaction of relaxin peptides is accompanied by side reactions which render the S-sulfo peptides difficult to purify resulting in low yields.

Using the above conditions chain combination yields from 1.5 to 6.0% have been achieved as measured by biological activity in the rat uterine contractility assay of Wiqvist & Paul (Acta Endocrinol., 29, 135-136, 1958).

Example of Chain Combination Reaction

Human relaxin H2 [S-thioethyl $Cys^{10,11,15}$] A(1-24) (4.2 mg dry wt., 2.4 mg peptide by amino acid analysis, 0.84 µmole) was dissolved in 500 µl of 0.1M glycine buffer pH 10.5 in a 3 ml stoppered plastic centrifuge tube. Human relaxin H2 [S-sulfo $Cys^{10,11}$] B(-1-24) (1.60mg, 1.60 mg peptide by amino acid analysis, 0.33 µmole) dissolved in 200 µl of 0.1M glycine buffer pH 10.5 was added and the mixture agitated. An aliquot (23.0 µl, 2.21 µmole DTT) of a stock solution of dithithreitol (DTT) made up in 0.1 M glycine buffer pH 10.5 (0.96 µmole DTT in 10 µl) was added to the peptide solution and following a brief agitation the reaction mixture was allowed to stand at 4°C for 24 hours open to the air. The mixture was then centrifuged and

aliquots of the supernatant solution tested for relaxin biological activity in the rat uterine contractility assay. Aliquots of the reaction mixture inhibited the spontaneous contractions of the rat uterus in a dose-related manner. A 75 µl aliquot completely inhibited uterine contractions equivalent to a chain combination yield of 5.3% as compared to a native pig relaxin A22 B31 standard.

Synthesis of authentic human relaxin H2 : hRLX A(1-24) - B(-1-32)

(i) Synthesis of full length H2 human relaxin B-chain :hRLX B(-1-32)

The amino acid sequence corresponding to residues -1 to +32 of the full length H2 human relaxin B-chain was synthesised using the procedures described above and commencing with 6.4 gm N-α-tertiarybutyloxy-carbonyl-L-leucine phenyl acetamido methyl polystyrene resin with a loading of 0.23 mmol Leu per gm. The side-chain protecting groups used for the A(1-24) and B(-1 - 24) peptides were also employed for the full length B-chain including the S-ethyl mercapto derivative for both cysteines at positions 10 and 22. A modification of this strategy was the use of the N-formyl derivative of BOC-L-tryptophan for coupling at sequence positions 27 and 2.

The final weight of the peptide-resin following chain assembly was 8.2gm. A portion of the peptide resin (4.0gm) was treated with anhydrous hydrogen fluoride-anisole as described in previous examples to yield 1.50gm of crude [S-thioethyl $Cys^{10,22}$, N-formyl

$Trp^{2,27}$] hRLX B(-1 - 32). The crude peptide was purified by gel filtration on BioGel P6 in 0.1M acetic acid. The major peaks eluting from the gel filtration column were characterised by amino acid analysis. The fractions with analyses consistent with the -1 to +32 peptide sequence were collected and lyophilised. Deformylation of the tryptophan residues was effected by treating the peptide (100mg) with sodium hydroxide solution (5ml) pH 11.5 for 5 min. during which time the peptide precipitated from solution. The reaction mixture was neutralised to dissolve the peptide and applied directly to a BioGel P6 column in 0.1M acetic acid. Removal of the formyl groups from tryptophan was monitored by UV spectroscopy by following the disappearance of the N-formyl absorption at 300 nm and the appearance of the characteristic tryptophan spectra with an absorption maximum at 280 nm. Peptide fractions eluting from the column with the correct amino acid anlysis were collected and lyophilised.

Attempts to further purity the [S-thioethyl $Cys^{10,22}$] hRLX B(-1 - 32) peptide by preparative HPLC were not successful because of loss of peptide by adsorption to the column media. Peptide purified by gel chromatography was used directly in chain combination experiments.

(ii) <u>Chain combination of A(1-24) with B(-1 - 32) : preparation of human relaxin H2</u>

The synthetic S-sulfonated and S-thioethyl H2 human relaxin A(1-24) peptides were coupled to S-thioethyl H2 human relaxin B(-1 - 32) using the same chain combination procedures described previously for

the shortened B-chain (-1 - 24). Samples of the recombination mixture were tested for relaxin biological activity in the rat uterine contractility assay. Aliquots of the reaction mixture inhibited the spontaneous contractions of the rat uterus in a dose-related manner. A 100µl aliquot completely inhibited uterine contractions equivalent to a chain combination yield of 3.0% as compared to a native pig relaxin A22 B31 standard.

The features disclosed in the foregoing description, in the following claims and/or in the accompanying drawings may, both separately and in any combination thereof, be material for realising the invention in diverse forms thereof.

References

Anderson, M.L., Long, J.A. and Hayashida, T. Immunofluorescence studues on the localisation of relaxin in the corpus luteum of the pregnant rat. Biol. Reprod. 13, 499-504 (1975).

Beaucage, S.L. and Caruthers, M.H. Tetrahedron Lett. 22, 1859-1862 (1981).

Chang, A.C.Y. Nature 275, 617-624 (1978).

Chirgwin, J.M., Przybyla, A.E., MacDonald, R.J. and Rutter, W.J., Isolation of biologically active ribonucleic acid from sources enriched in ribonuclease. Biochem. 18, 5294-5299, (1979).

Haley, J., Hudson, P., Scanlon, D., John, M., Cronk, M., Shine, J., Tregear, G. and Niall, H. DNA 1, 155-162 (1982).

Hisaw, F.L. Proc. Soc. Exp. Biol. Med. 23, 661-663 (1926).

Hudson, P., Haley, J., Cronk, M., Shine, J. and Niall, H. Nature, 291, 127-131 (1981).

Hudson, P., Haley, J., John, M. Cronk, M., Crawford, R., Haralambidis, J., Tregear, G., Shine, J. and Niall, H. Structure of a genomic clone encoding biologically active human relaxin. Nature 301, 628-631 (1983).
Huynh, T., Saint, R. and Davis, R. (1983) personal communication.

James, R., Niall, H., Kwok, S. and Bryant-Greenwood, G. Nature, 267, 544-546 (1977).

John, M.J., Walsh, J.R., Borjesson, B.W. and Niall, H.D. Endocrinology 108, 726-729 (1981).

Lawn, R.M., Fritsch, E.F., Parker, R.C., Blake, G. and Maniatis, T. all 15, 1157-1174 (1978).

Maxam, A.M. and Gilbert, W. (1977) A new method for sequencing DNA. Proc. Natl. Acad. Sci. USA 74, 560-564.

Morrison, D.A., In: Methods in Enzymology, R. Wu, ed. (New York : Academic Press) pp. 326-331 (1979).

Roychoudbury, R. Jay, E. and Wu, R. (1976) Terminal labelling and addition of homopolymer tracts to duplex DNA fragments by terminal deoxy-nucleotidyl transferase. Nucleic Acid Res. 3, 863-877 (1976).

Sanger, F., Coulson, A.R., Barrell, B.G., Smith, A.J.H. and Roe, B.A., J. Mol. Biol. 143, 161-178 (1989).

Schwabe, C., Gowan, L.K. and Reinig, J.W., Ann. N.Y. Acad. Sci. 380, 6-12 (1982).

Schwabe, C., McDonald, J.K. and Steinetz, B.C. Biochem. Biophys. Res. Commun. 75, 503-510 (1977).

Southern, E.M., J. Mol. Biol. 98, 503-517 (1975).

Taylor, J.M., Illmersee, R., and Summers, J.Biochim. Biophys. Acta 442, 324-330 (1976).

Ullrich, A., Shine, J., Chirgwin, J., Picket, R., Tischer, E., Rutter, W.J. and Goodman, H.M. Rat insulin genes: construction of plasmids containing the coding sequences. Science 196, 1313-1319 (1977).

Vogt, V.M. Purification and further properties of single-strand-specific nuclease from Aspergillus oryzae. Eur. J. Biochem. 33, 192-200 (1973).

Wickers, M.P., Buell, G.N. and Schimke, R.T. Synthesis of double-stranded Dna complementary to lysozyme, ovomucoid, and ovalbumin mRNAs. J.Biol. Chem. 253, 2483-2495 (1978).

CLAIMS:

1. A gene for the expression of human H2-preprorelaxin, or a sub-unit thereof or an equivalent of such a gene or sub-unit.

2. A double-stranded DNA fragment for the expression of human H2-preprorelaxin, characterized in that it comprises a coding strand and a complementary strand corresponding to the following complete mRNA sequence:

AUG CCU CGC CUG UUU UUU UUC CAC CUG CUA GGA GUC UGU UUA
CUA CUG AAC CAA UUU UCC AGA GCA GUC GCG GAC UCA UGG AAG
GAG GAA GUU AUU AAA UUA UGC GGC CGC GAA UUA GUU CGC GCG
CAG AUU GCC AUU UGC GGC AUG AGC ACC UGG AGC AAA AGG UCU
CUG AGC CAG GAA GAU GCU CCU CAG ACA CCU AGA CCA GUG GCA
GAA AUU GUA CCA UCC UUC AUC AAC AAA GAU ACA GAA ACU AUA
AAU AUG AUG UCA GAA UUC GUU GCU AAU UUG CCA CAG GAG CUG
AAG UUA ACC CUG UCU GAG AUG CAG CCA GCA UUA CCA CAG CUA
CAA CAA CAU GUA CCU GUA UUA AAA GAU UCC AGU CUU CUC UUU
GAA GAA UUU AAG AAA CUU AUU CGC AAU AGA CAA AGU GAA GCC
GCA GAC AGC AGU CCU UCA GAA UUA AAA UAC UUA GGC UUG GAU
ACU CAU UCU CGA AAA AAG AGA CAA CUC UAC AGU GCA UUG GCU
AAU AAA UGU UGC CAU GUU GGU UGU ACC AAA AGA UCU CUU GCU
AGA UUU UGC UGA

or a sub-unit thereof or an equivalent of such a sequence or sub-unit.

3. A sub-unit of the gene claimed in Claim 1, which is a gene for the expression of human H2-prorelaxin or an equivalent of such a gene.

4. A sub-unit of the double stranded DNA fragment claimed in Claim 2, which is a double-stranded DNA fragment for the expression of human H2-prorelaxin, characterized in that it comprises a coding strand and a complementary strand corresponding to the following mRNA sequence:

GAC UCA UGG AAG GAG GAA GUU AUU AAA UUA UGC GGC CGC GAA
UUA GUU CGC GCG CAG AUU GCC AUU UGC GGC AUG AGC ACC UGG
AGC AAA AGG UCU CUG AGC CAG GAA GAU GCU CCU CAG ACA CCU
AGA CCA GUG GCA GAA AUU GUA CCA UCC UUC AUC AAC AAA GAU
ACA GAA ACU AUA AAU AUG AUG UCA GAA UUC GUU GCU AAU UUG
CCA CAG GAG CUG AAG UUA ACC CUG UCU GAG AUG CAG CCA GCA
UUA CCA CAG CUA CAA CAA CAU GUA CCU GUA UUA AAA GAU UCC
AGU CUU CUC UUU GAA GAA UUU AAG AAA CUU AUU CGC AAU AGA
CAA AGU GAA GCC GCA GAC AGC AGU CCU UCA GAA UUA AAA UAC
UUA GGC UUG GAU ACU CAU UCU CGA AAA AAG AGA CAA CUC UAC
AGU GCA UUG GCU AAU AAA UGU UGC CAU GUU GGU UGU ACC AAA
AGA UCU CUU GCU AGA UUU UGC UGA

or an equivalent of such a sequence.

5. A sub-unit of the gene claimed in Claim 1, which is a gene for the separate expression of the signal, A, B or C peptide chains of human H2-relaxin or any combination of two or more of the said chains.

6. A sub-unit of the double stranded DNA fragment claimed in Claim 2, which is a double-stranded DNA fragment for the expression of the signal peptide, A, B or C peptide chains of human H2-preprorelaxin or a combination of any two or more of said chains characterized in that it comprises a coding strand and a complementary strand corresponding to the appropriate

mRNA sequence or combination of the mRNA sequences given below:

Signal Peptide

AUG CCU CGC CUG UUU UUU UUC CAC CUG CUA GGA GUC UGU UUA CUA CUG AAC CAA UUU UCC AGA GCA GUC GCG

A-Chain

CAA CUC UAC AGU GCA UUG GCU AAU AAA UGU UGC CAU GUU GGU UGU ACC AAA AGA UCU CUU GCU AGA UUU UGC UGA

B-Chain

GAC UCA UGG AAG GAG GAA GUU AUU AAA UUA UGC GGC CGC GAA UUA GUU CGC GCG CAG AUU GCC AUU UGC GGC AUG AGC ACC UGG AGC AAA AGG UCU CUG

C-Chain

AGC CAG GAA GAU GCU CCU CAG ACA CCU AGA CCA GUG GCA GAA AUU GUA CCA UCC UUC AUC AAC AAA GAU ACA GAA ACU AUA AAU AUG AUG UCA GAA UUC GUU GCU AAU UUG CCA CAG GAG CUG AAG UUA ACC CUG UCU GAG AUG CAG CCA GCA UUA CCA CAG CUA CAA CAA CAU GUA CCU GUA UUA AAA GAU UCC AGU CUU CUC UUU GAA GAA UUU AAG AAA CUU AUU CGC AAU AGA CAA AGU GAA GCC GCA GAC AGC AGU CCU UCA GAA UUA AAA UAC UUA GGC UUG GAU ACU CAU UCU CGA AAA AAG AGA

or an equivalent of such a sequence.

7. A process for the isolation of a relaxin gene of a human or other primate or a related species

characterized in that it comprises using as a probe a sub-unit of the human H1-relaxin gene.

8. A process for the production of a gene or an equivalent thereof or a sub-unit thereof as set out in any one of Claims 1 to 6, characterized in that it comprises screening a human cDNA clone bank using as a probe a fragment of human H1-relaxin DNA.

9. A process as claimed in Claim 8, characterized in that the said fragment comprises nucleotides of C-peptide/A-peptide coding region of the human H1-relaxin DNA.

10. A DNA transfer vector, characterized in that it contains a cDNA deoxynucleotide sequences corresponding to a gene as defined in any one of Claims 1 to 6 or a sub-unit of such a gene or an equivalent of such a gene or sub-unit.

11. A gene or DNA transfer vector as claimed in any one of Claims 1 to 6 and 10, characterized in that one or more natural codons or their cDNA equivalents are replaed by another codon which codes for the same amino-acid.

12. A gene or DNA transfer vector as claimed in any one of Claims 1 to 6 and 10, characterized in that one or more of the natural codons are deleted and/or are replaced by codons which code for amino acids other than that code by the natural codon, and/or further codons are added to the natural sequence.

13. A DNA transfer vector as claimed in any one of Claims 1 to 6 and 10 to 12, characterized in that it is a bacterial plasmid.

14. A DNA transfer vector as claimed in any one of Claims 1 to 6 and 10 to 12, characterized in that it is a bacteriorphage DNA.

15. A cell transformed by a transfer vector as claimed in any one of Claims 10 to 14.

16. A process for making a DNA transfer vector for use in maintaining and replicating a deoxynucleotide sequence coding for human H2-preprorelaxin or a sub-unit thereof, characterized in that it comprises reacting the appropriate deoxynucleotide sequence of human H2-preprorelaxin or the sub-unit with a DNA molecule prepared by cleaving a transfer vector with a restriction enzyme.

17. A process for making a fusion protein comprising an amino acid sequence consisting of all or part of the amino acid sequence of human H2-preprorelaxin as its C-terminal sequence and a portion of a procaryotic protein as its N-terminal sequence, characterised in that it comprises incubating a microorganism transformed by an expression transfer vector comprising the appropriate deoxynucleotide sequence.

18. A process for synthetizing human H2-prorelaxin comprising the A and B peptides separated from each other by a C peptide, characterized in that it comprises incubating a microorganism, transformed by an expression transfer vector comprising a deoxynucleotide sequence

coding for said human prorelaxin under conditions suitable for expression of said sequence coding for human prorelaxin, and purifying human prorelaxin from the lysate or culture medium of said microorganism.

19. A fusion protein comprising an amino acid sequence characterized in that it consists of all or part of the amino acid sequence of human H2-preprorelaxin as its C-terminal sequence and a portion of a procaryotic protein as its N-terminal sequence.

20. Synthetic human H2-preprorelaxin.

21. Synthetic human H2-prorelaxin.

22. Synthetic human H2-relaxin.

23. The synthetic signal A, B or C peptide chains of human H2-preprorelaxin.

24. A human H2-relaxin analogue characterized in that it consists essentially of shortened and/or modified forms of the natural B and/or A peptide chains.

25. A human H2-relaxin analogue, characterized in that one or both of A and B chains in the full length or shortened form is modified by the addition of a protective group to a free amino group.

26. An analogue as claimed in Claim 24, characterized in that the modification comprises the replacement of at least one of the natural amino-acids in one or both of the A and B chains with a different amino acid.

27. An analogue as claimed in Claim 24, characterized in that the modification comprises the deletion of at least one of the natural amino-acids from one or both of the A and B chains and/or the addition of at least one extra amino-acid to one or both of the natural A and B chains.

28. An analogue as claimed in Claim 24, characterized in that the A-chain is shortened by up to 9 amino-acids at the amino terminus and/or the B-chain is shortened by up to 9 amino-acids at the amino terminus and up to 9 amino-acids at the carboxyl terminus.

29. An analogue as claimed in Claim 27, characterised in that it consists of any one of the A-chains A(1-24), A(2-24), A(3-24) in combination with any one of the B-chains B(1-23) to B(1-32).

30. A process for preparing human H2-relaxin or an analogue thereof, characterized in that the A and B chains of relaxin in their full-length, modified or shortened forms are combined by a method known per se for combination of the A and B chains of insulin.

31. A process for preparing human H2-relaxin or an analogue thereof, characterized in that the A and B chains of relaxin in their full-length, modified or shortened forms are combined by reducing a mixture of the S-sulfonated and/or S-thioalkylated A and B chains, allowing the mixture to oxidize in air and recovering the relaxin or relaxin analogue thus produced.

32. A process for preparing human H2-relaxin or an analogue from human H2-prorelaxin or an analogue

thereof, characterized in that the sulfhydryl groups on the A and B peptide chains are converted to disulfide cross-links between said A and B peptides and the C-peptide is then excised.

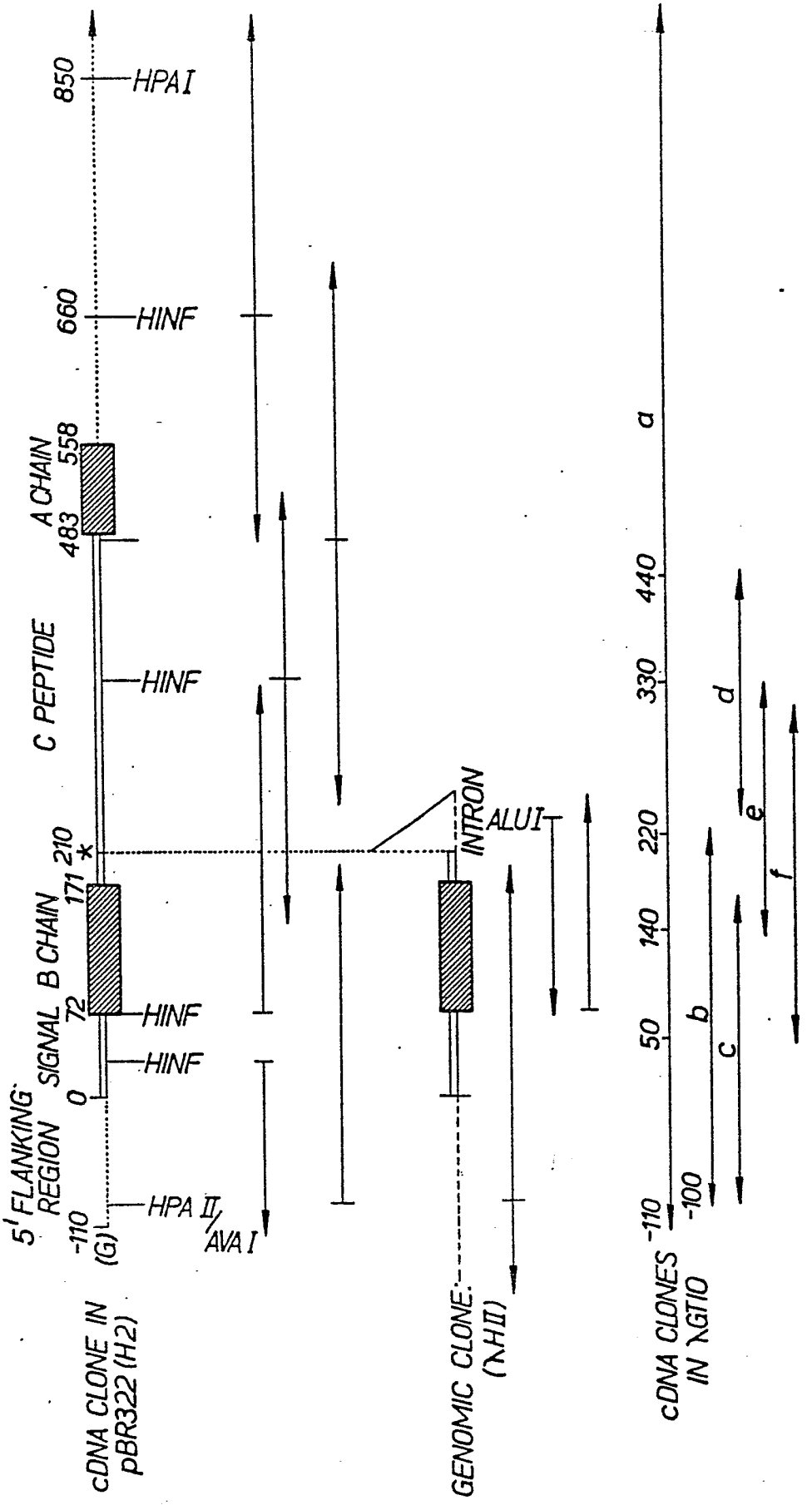

850
HPA I
660
HINF
558
A CHAIN
483
HINF
C PEPTIDE
210
*
171
B CHAIN
SIGNAL
72
HINF
HINF
0
5' FLANKING REGION
-110
(G)
HPA II/
AVA I
cDNA CLONE IN pBR322 (H2)
INTRON
ALU I
GENOMIC CLONE (λ H II)
a
440
330
d
220
e
140
f
50
b
c
-100
-110
cDNA CLONES IN λGT10

FIG. 1.

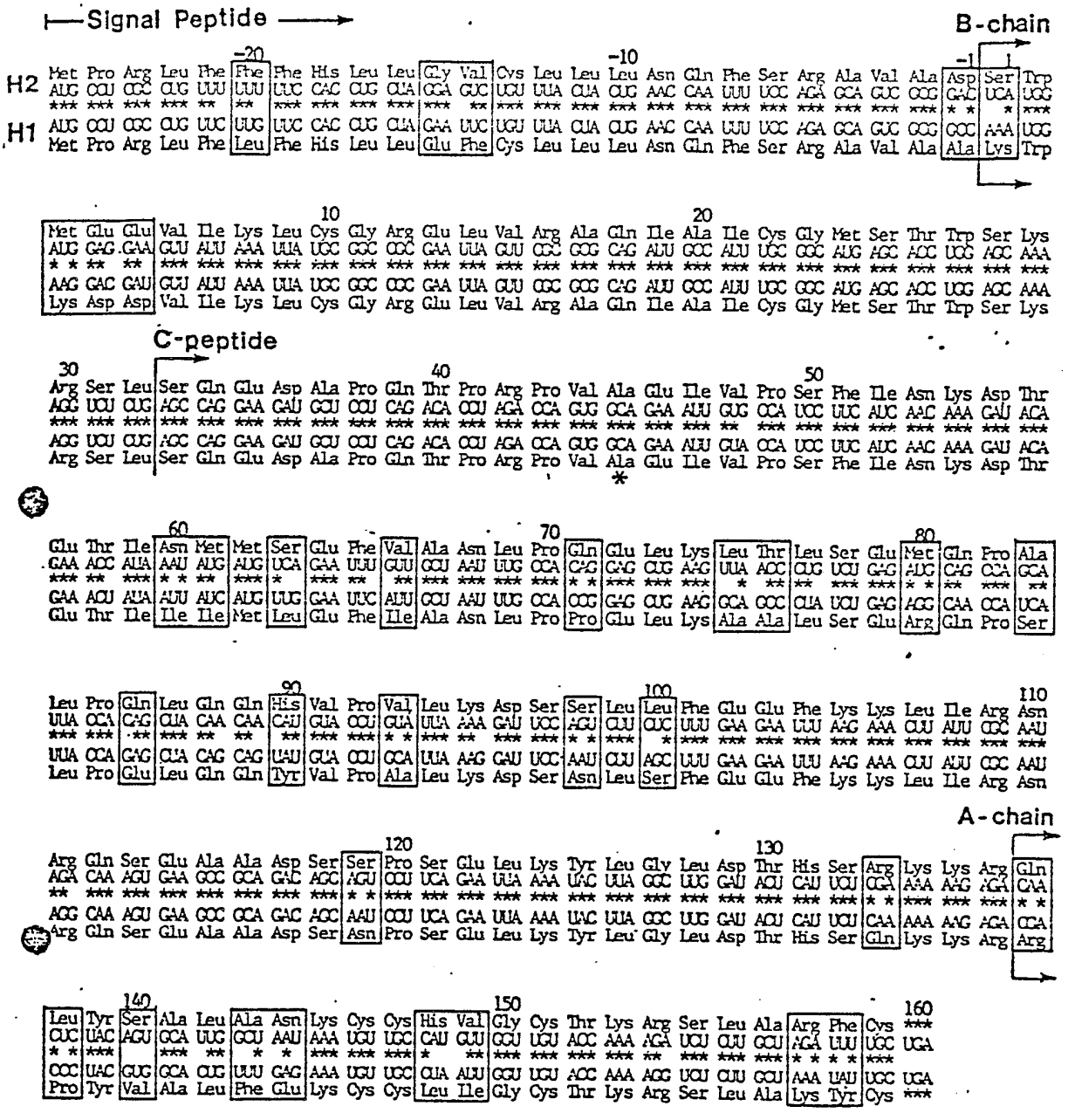


FIGURE 2.

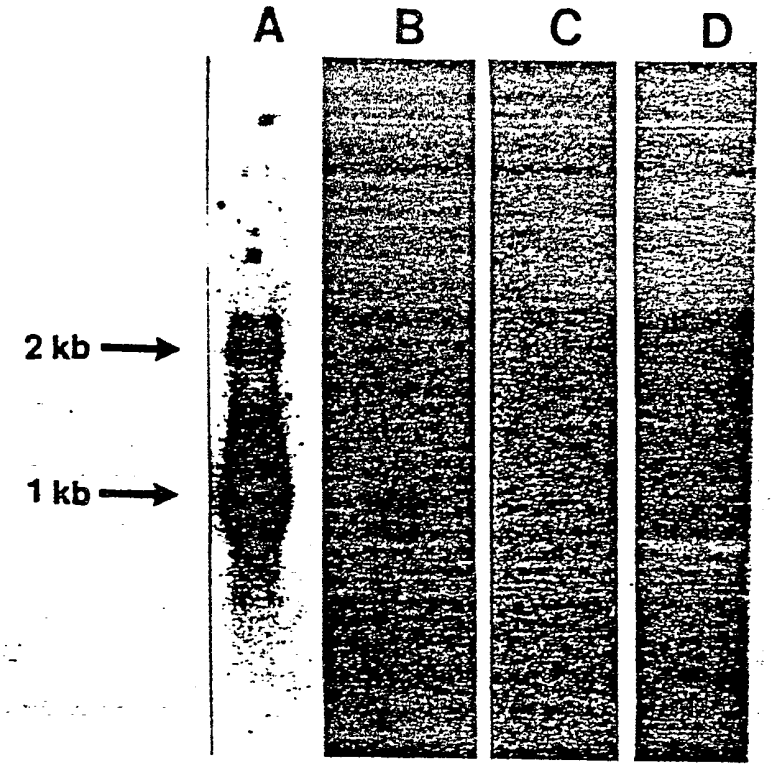


FIG. 3a.

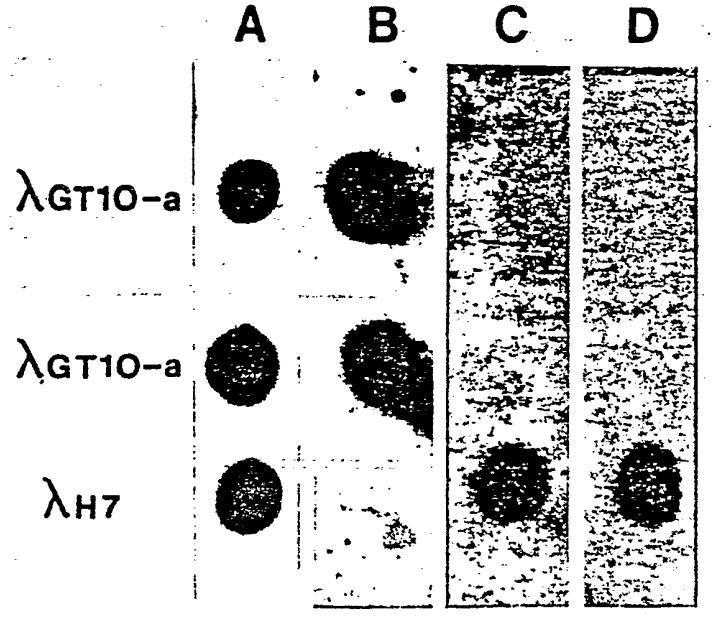


FIG. 3b.

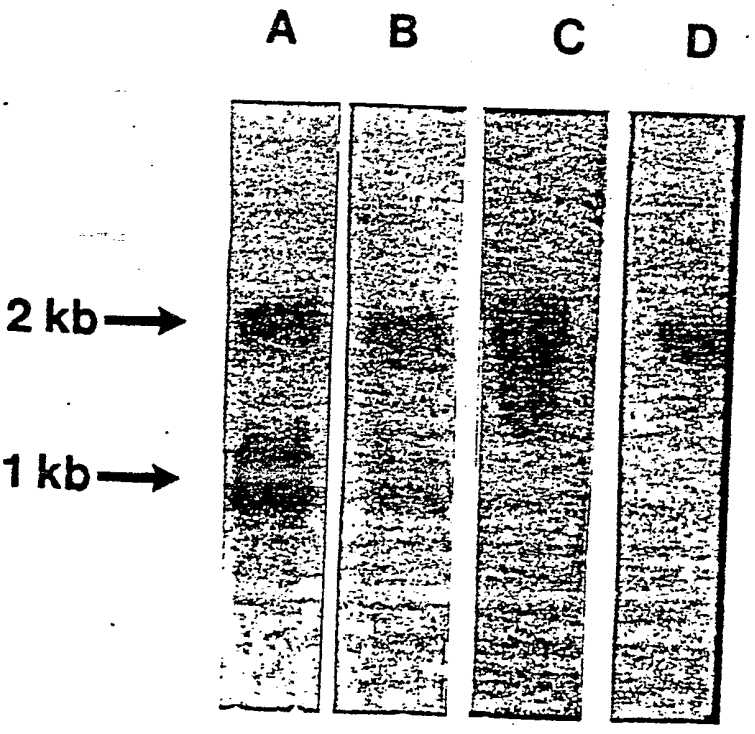


FIG. 4.

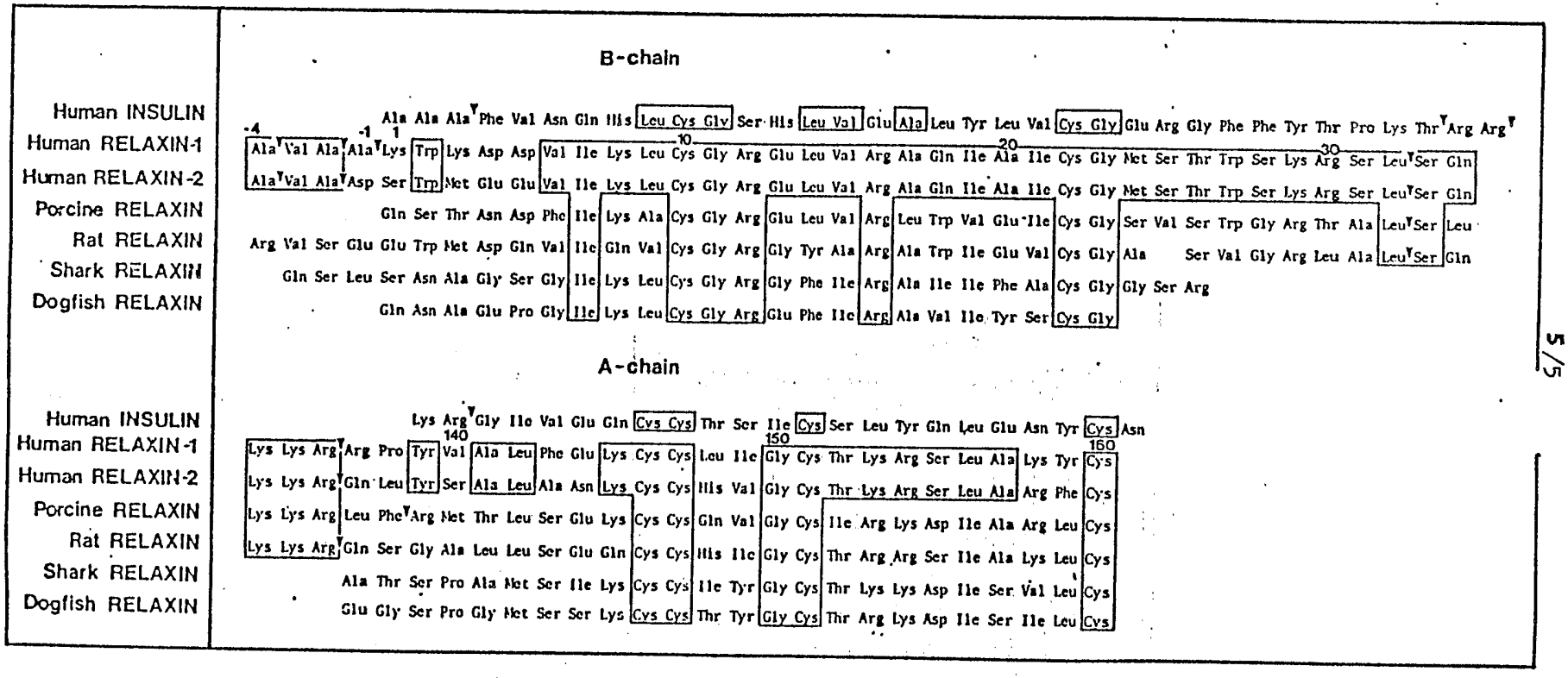


FIGURE 5.

0112149

.DNA
Volume 1, Number 2, 1982
Mary Ann Liebert, Inc., Publishers

Porcine Relaxin: Molecular Cloning and cDNA Structure

J. HALEY, P. HUDSON, D. SCANLON, M. JOHN, M. CRONK,*
J. SHINE,* G. TREGEAR, and H. NIALL

ABSTRACT

Relaxin is a peptide hormone produced by the corpora lutea of ovaries during pregnancy, softening and lengthening the ligaments of the pelvis and softening the cervix in order to make childbirth easier. In attempts to determine the nucleotide sequence coding for relaxin, recombinant DNA techniques were used to obtain a cDNA clone bank from total mRNA isolated from the ovaries of pigs in late pregnancy. Clones were screened using cDNA initiated by synthetic oligonucleotide primers coding for the Trp Val Glu Ile sequence of the porcine relaxin B chain. The synthetic undecamer [5'-ATCTCCACCCA-3'] was found to prime a specific ^{32}P-labeled cDNA of approximately 300 nucleotides containing B chain and signal peptide coding sequences, as verified by nucleic acid sequence analysis. This cDNA was used to probe the ovarian clone bank. Several clones containing large inserts which hybridized to this probe were subjected to sequence analysis and some of these were found to contain the preprorelaxin coding region, comprising a signal peptide of 24 amino acids, a B chain of 32 amino acids, a large C peptide of 104 amino acids, and an A chain of 22 amino acids. From the amino acid sequence of prorelaxin derived in this way, it appears that the processing of prorelaxin involves two enzymes with chymotrypsin-like and trypsin-like specificity, respectively. In comparisons of porcine and rat preprorelaxins, the C region had as much amino acid sequence homology as the B and A chains. The C region is also rich in charged amino acids, suggesting a role for it beyond simply ensuring proper disulfide bond formation.

INTRODUCTION

Relaxin is a peptide hormone of interest in mammalian reproductive physiology for its critical role in the softening of the cervix and pubic symphysis prior to parturition (Hisaw, 1926). Amino acid sequence analysis has unequivocally demonstrated the presence of relaxin in the ovaries of the rat (John *et al.*, 1981), pig (Schwabe *et al.*, 1977; James *et al.*, 1977), and, curiously, shark (Schwabe *et at.*, 1978). Like insulin, it comprises a two-chain structure, linked by disulfide bonds, and is derived from a single-chain precursor by several processing steps. Rat preprorelaxin has been shown to contain a 105 amino acid connecting peptide linking the A and B chains (Hudson *et al.*, 1981). Cell-free translations of mRNA isolated from the ovaries of pregnant pigs and immunoprecipitation of the protein products with relaxin antisera also suggested a large relaxin precursor of about 23,000 daltons as compared to 11,000 daltons for preproinsulin (Gast *et al.*, 1980). It thus appeared likely that the pig relaxin precursor would be similar in structure to that of the rat with a large connecting peptide joining the A and B chains.

To study the structure of pig preprorelaxin we have used recombinant DNA techniques to construct *E. coli* cDNA clones containing sequences complementary to the total mRNA population of pig ovarian corpora lutea. However, limited amino acid sequence homology exists between rat and pig relaxins (John *et al.*, 1981), and we have found that no significant cross hybridization occurs between the rat relaxin cDNA, available from earlier studies (Hudson *et al.*, 1981) and the pig cDNA clones.

Consequently, we used chemically synthesized oligonucleotide primers to prepare pig relaxin-specific cDNA, which, in turn, was used as a probe to isolate cDNA clones containing pig preprorelaxin coding sequences. We report here the primary structure of the entire pig preprorelaxin coding sequence determined from analysis of the recombinant cDNA clones.

MATERIALS AND METHODS

Terminal transferase was purchased from Ratcliff Biochemicals (Los Alamos, NM). *Pst* I, *Bgl* II, DNA polymerase (Klenow fragment), and Sl nuclease were from Boehringer Mannheim. *Hinf* I, *Taq* I, *Hae* III, *Alu* I, and T_4 DNA ligase were from New England Biolabs (Beverly, MA). Oligo-dT cellulose type 7 was obtained from PL Biochemicals (Milwaukee, WI). ^{32}P-labeled nucleoside triphosphates and ^{35}S-labeled amino acids were from Amersham. Reverse transcriptase was the gift of Dr. J. Beard (Life Sciences, St. Petersberg, FL). M13 bacteriophage and M13 primers were the gifts of Dr. J. Messing and Dr. R. Crea, respectively.

Howard Florey Institute of Experimental Physiology and Medicine, University of Melbourne, Parkville, Victoria, Australia 3052.
*Department of Genetics, Research School of Biological Sciences, Australian National University, Canberra, A.C.T., Australia 2601.

Messenger RNA isolation

Ovaries from pigs in late pregnancy were obtained by collection at abattoirs and quickly frozen on dry ice. The corpora lutea were dissected free of other tissue, the RNA isolated in 5 *M* guanidinium thiocyanate (Merck) (Chirgwin *et al.*, 1979) and the poly A⁺ containing RNA purified by oligo-dT cellulose affinity chromatography (Aviv and Leder, 1972). Yields were approximately 10 μg poly A⁺ RNA per 100 mg of tissue. To assay mRNA for relaxin-containing message, cell-free translations were carried out employing rabbit reticulocyte lysate (Pelham and Jackson, 1976), and immunoprecipitated proteins (Kessler, 1975) were electrophoresed on SDS polyacrylamide gels (Studier, 1973).

cDNA was prepared using reverse transcriptase and an oligo-dT primer (Wickers *et al.*, 1978), the RNA hydrolyzed in alkali, and the cDNA made double stranded (Ullrich *et al.*, 1977) with DNA polymerase I (Klenow fragment). The single-stranded hairpin loop was removed with 10 units of S1 nuclease at 20°C for 5 min (Vogt, 1973).

Homopolymeric deoxycytidine extensions were enzymatically added using terminal transferase (10 units in 50 μl reaction volume at 37°C for 10 min) in a controlled reaction designed to add approximately 30 C-residues to the 3'-OH ends (Roychoudbury *et al.*, 1976). This tailed cDNA was annealed to the plasmid pBR322 which had been cleaved with *Pst* I and similarly tailed with G-residues. The recombinant plasmids were used to transform *E. coli* RRI (efficiency is 10^5 clones per μg plasmid) and clones containing ovarian cDNA were selected on the basis of tetracycline resistance (Morrison, 1979).

Selection of specific cDNA clones

To screen the ovarian cDNA clone bank for relaxin-specific sequences, eight 11-base primers were chemically synthesized by the phosphotriester method (Itakura *et al.*, 1973) to make all possible complementary sequences corresponding to the peptide sequence Trp–Val–Glu–Ile in the pig relaxin B chain (Fig. 1). These primers were used to select specific cDNA products for use as hybridization probes to the cDNA clone bank.

Oligonucleotide primers were used to initiate reverse transcription of mRNA under conditions designed for the synthesis of high specific activity and yet full length cDNA. Two micrograms of mRNA were added to between 0.1 and 1 μg of primer, heated to 90°C for 2 min, slowly cooled, and the reverse transcriptase reaction carried out at 37°C in 50 m*M* Tris pH 8.0, 50 m*M* NaCl, 10 m*M* $MgSO_4$, 0.1 m*M* DTT with 600 μ*M* dATP, dTTP, and dGTP, 30 μM dCTP, 30 μCi α-^{32}P-dCTP, and 10 units of reverse transcriptase. Reaction products were alkali treated (100 m*M* NaOH, 80°C, 10 min) to remove RNA and analyzed on 6% acrylamide 7 *M* urea gels for the presence of pregnancy-specific cDNAs (Fig. 2).

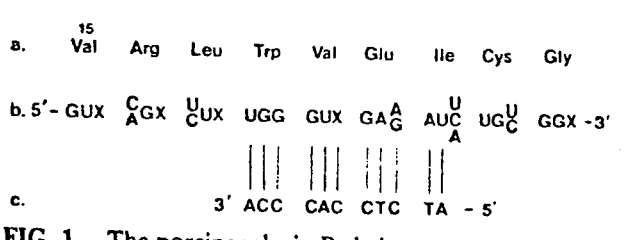


FIG. 1. The porcine relaxin B chain sequence formed the basis for the synthesis of eight oligonucleotide primers which were used to hybridize specifically to porcine relaxin mRNA. (a) Amino acids 15–23 of the porcine relaxin B chain; (b) the possible nucleotide sequences of the mRNA corresponding to the amino acid sequence, where X represents any base; (c) primer actually used to initiate relaxin specific cDNA synthesis.

In order to identify which of the cDNA clones contained relaxin-specific sequences, in a separate experiment the primer (lacking the 5' phosphate) was radiochemically end-labeled with T4 polynucleotide kinase and γ-^{32}P-ATP (100 μCi per μg primer) and the cDNA synthesized in the absence of α-^{32}P-deoxynucleotide (Noyes *et al.*, 1979). This yielded end-labeled DNA that was sequenced partially by the chemical degradation technique (Maxam and Gilbert, 1977). To do this, the regions of the gel corresponding to specific cDNA bands were excised, placed in dialysis membrane bags, and the DNA electrophoretically removed from the gel matrix in 50 m*M* Tris-borate, 1 m*M* EDTA (pH 8.1). Eluted DNA samples were precipitated with 2 volumes of ethanol in 0.3 *M* Na acetate (pH 5.5) at -20°C for 4 h. before performing the chemical degradation reactions. A 300 nucleotide fragment was found in this way to contain prorelaxin cDNA.

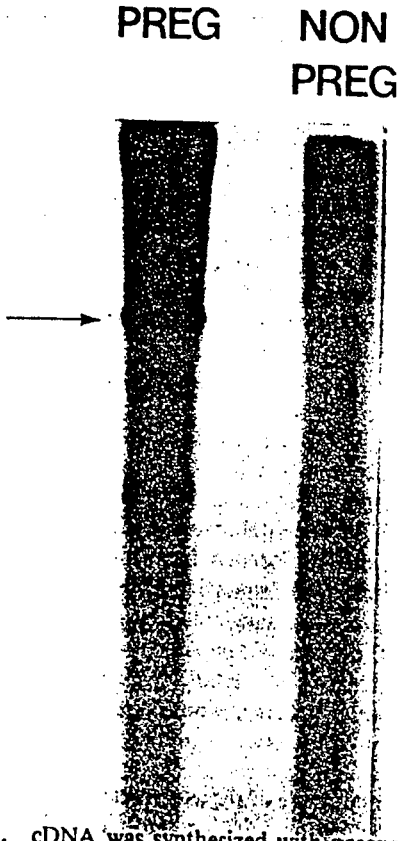


FIG. 2. cDNA was synthesized with pregnant and non-pregnant ovarian mRNA with the use of the primer shown in Fig. 1(c) and analyzed on 6% polyacrylamide 7 *M* urea gels as described in Materials and Methods. The arrow indicates the approximately 300 nucleotide ^{32}P-labeled cDNA found to contain the coding sequence for the porcine relaxin B chain and signal peptide.

The relaxin-specific cDNA fragment identified by the methods described above was synthesized to a specific activity greater than 10^8 cpm/μg, purified on polyacrylamide gels, and used to screen the cDNA clone banks (Thayer, 1979). Colonies which hybridized to this probe were rescreened in duplicate in order to grade the positives as to their rate of specific hybridization. The strongest hybridizing clones were screened by a rapid plasmid isolation procedure (Holmes and Quigley, 1981) and those containing the largest recombinant plasmids were grown in 1 liter cultures for large-scale plasmid isolation (Tanaka and Weisblum, 1975) yielding about 700 μg of plasmid.

Sequence analysis of recombinant plasmids

Restriction digests were carried out under the conditions specified by New England Biolabs. Purified DNA fragments with 5'-protruding ends were end-labeled using reverse transcriptase and the appropriate α-labeled deoxynucleotide triphosphase (dCTP for *Hpa* II and *Taq* I; dATP for *Hinf* I). 3'-protruding ends generated with *Pst* I were labeled using terminal transferase and [^{32}P]-cordycepin triphosphate. Fragments were separated by electrophoresis on 8% polyacrylamide gels and sequenced by the chemical degradation method (Maxam and Gilbert, 1977).

The cloned cDNA inserts released by *Pst* I digestion were also ligated into bacteriophage M13 mp9 or mp7.1 and the single-stranded template DNA isolated and sequenced using the dideoxy procedure (Sanger *et al.*, 1980). The M13 recombinants were sequenced using either the M13-specific primer or with specific primers chosen over particular regions of the internal relaxin sequence.

RESULTS

cDNA cloning and nucleotide sequence analysis

Polyadenylated RNA was isolated from corpora lutea dissected from the ovaries of pigs in late pregnancy. Since cell-free translation studies of this material had readily demonstrated a product immunoprecipitable by antirelaxin antisera it was expected that relaxin-specific mRNA would be present in abundant quantities. Hence in initial studies, cDNA from pregnant and nonpregnant pig ovaries was digested with restriction endonucleases in an attempt to find predominant pregnancy-specific fragments which might derive from relaxin cDNA. Since this approach was unsuccessful, it appeared that the level of relaxin mRNA was likely to be less than 1% of the total ovarian mRNA. This assumption was subsequently confirmed when it was found that the proportion of colonies containing relaxin sequences in a clone bank obtained from total pregnant corpora lutea was of the order of 0.3%

Another approach used to identify pig relaxin cDNA clones was to screen bacterial colonies containing recombinant plasmids with a probe made from cloned rat prepro-relaxin cDNA. However, specific cross hybridization was not observed even under conditions of relatively low stringency of hybridization. This result can now be interpreted in terms of the nucleotide sequence homology between rat and pig preprorelaxin cDNAs (presented below). While the overall homology (65%) might have allowed cross hydridization it can be seen that the longest region of nucleotide sequence identity uninterrupted by mismatches is only 13 bases.

In a third approach a series of oligodeoxynucleotides were synthesized on the basis of the known amino acid sequence of pig relaxin (Scanlon, 1981). Several of the primers initiated pregnancy-specific cDNA products, but these proved not to contain sequences coding for porcine relaxin. However, one of the synthetic oligonucleotides [5'-ATCTCCACCCA-3'] was found to initiate a pregnancy-specific cDNA of roughly 300 nucleotides (Fig. 2), whose sequence encoded the NH_2-terminal region of the relaxin B chain. Approximately 5000 *E. coli* ovarian cDNA clones were screened by *in situ* filter hybridization with the relaxin-specific cDNA probe and 15 colonies proved positive on rescreening (0.3% of the total clones); their plasmid inserts were isolated and sized on 1% agarose gels.

Several different *Pst* insert sizes were found, presumably caused by variation in either reverse transcription or in the S1 nuclease digestion of the hairpin loop during the double-stranding reaction. Three clones were selected for DNA sequence analysis. The restriction endonuclease map of relaxin cDNA determined from analysis of these three clones appears in Fig. 3 along with the sequencing strategy. Each of the inserts contained single *Hpa* II and *Hinf* I restriction sites; cleavage at these sites provided fragments for end-labeling and Maxam and Gilbert sequencing. For one of the clones, pRLX2, both DNA strands were sequenced with the exception of the A chain region and the 3'-untranslated region where clear sequence was obtained using two separate restriction fragments from the same strand. The 3'-untranslated region is 206 nucleotides in length beginning with the UGA termination codon at the end of the A chain. The DNA sequence of all three clones confirmed that the nucleotide sequence encoded the known A and B chain primary structure of porcine relaxin (Fig. 4). Regions corresponding to a C or connecting peptide and a signal peptide could be identified, giving an overall structure of the form: signal peptide–B chain–C peptide–A chain.

DISCUSSION

In the present work we have analyzed the nucleotide sequence of cloned cDNAs containing the structural gene sequence coding for pig preprorelaxin. The results allow us to predict the amino acid sequence of the signal peptide and of the connecting C peptide and to confirm the previously reported sequences of the B and A chains of pig relaxin (Schwabe *et al.*, 1977; James *et al.*, 1977; Niall *et al.*, 1980).

Only one initiation codon (AUG) was found 5' to the nucleotide sequence encoding the porcine relaxin B chain. The predicted signal peptide has 24 residues with a typical preponderance of hydrophobic amino acids. Cleavage of a glycine–glutamine bond would be involved in the removal of the signal peptide, presumably with concomitant (or subsequent) cyclization of the newly generated N-terminal amino acid (glutamine) to generate the pyroglutamic acid residue known to be at the blocked N-terminus of the pig relaxin B chain (James *et al.*, 1977; Schwabe *et al.*, 1977). The size of the signal peptide is consistent with earlier predictions made on the basis of *in vitro* translation studies (Gast *et al.*, 1980).

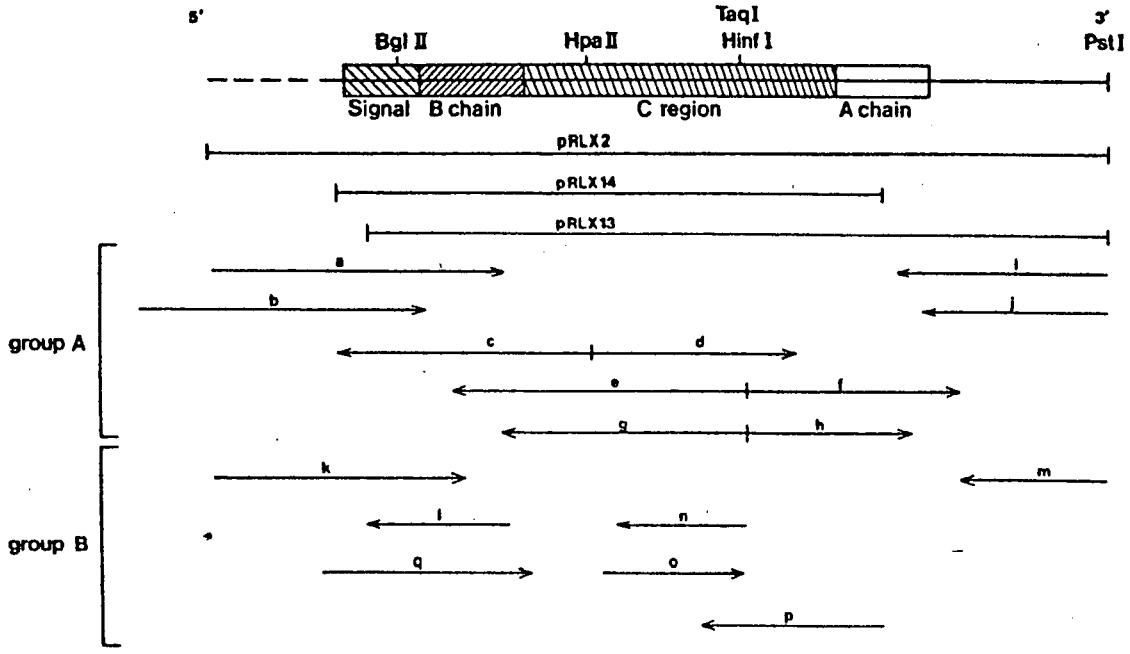


FIG. 3. The restriction map and sequencing strategy of three clones containing relaxin cDNA, pRLX2, pRLX13, and pRLX14, indicating the length of each clone relative to the composite structure. Group A represents those sequences derived by the Maxam and Gilbert method (the asterisk marks the position of the ^{32}P-end label). (a) **Pst* I–*Hpa* II; (b) **Hpa* II–*Bgl* II; (c) *Pst* I–*Hpa* II*; (d) **Hpa* II–*Pst* I; (e) *Pst* I–*Taq* I*; (f) **Taq* I–*Pst* I; (g) *Pst* I–*Hinf* I*; (h) *Hinf I–*Pst* I; (i) *Hinf* I–*Pst* I*; (j) *Hinf* I–*Hpa* II*. Group B represents those sequences derived by subcloning restriction fragments into the appropriate sites of bacteriophage M13 mp7.1 and mp9; (k,l,m,p,q) were *Pst* I fragments; (n,o) were *Hpa* II–*Taq* I fragments subcloned into the *Acc* I site. Recombinant plaques were sequenced using an M13-specific primer by the dideoxy procedure of Sanger *et al.* (1980) except (l) which was primed with the relaxin-specific B-chain primer [5'-ATCTCCACCCA-3'].

Several forms of porcine relaxin have been isolated with an identical A chain of 22 amino acids and B chains which vary in length from 29 to 31 amino acids (Sherwood and O'Byrne, 1974). The predominant relaxin molecule isolated when procedures designed to minimize degradation are used has a B chain of 31 amino acids. From this it appears that the shorter B chain forms are generated artifactually during extraction and purification. However, studies using carboxypeptidases suggest that there is a small quantity of a form of relaxin with a leucine residue at the carboxyl terminus (Niall *et al.*, 1980). The nucleotide sequence confirms the presence of a leucine at position B32. If this B32 relaxin is taken to be the largest form of the native hormone, the connecting (C) region can be defined as comprising 104 amino acids extending from residue 33 to residue 136 (inclusive) of prorelaxin (Fig. 4). It may be preferable for the present to refer to a C region rather than a C peptide since the sequence of processing steps involved in generating relaxin from prorelaxin is not yet known and there is no evidence as yet that a single C peptide exists as a defined molecular entity.

The A chain extends from residue 137 (arginine) to residue 158 (cysteine), the codon for which is followed immediately by a termination codon (UGA). Thus the coding region of the mRNA for porcine preprorelaxin specifies a translation product of 182 amino acids consisting successively of a signal peptide of 24 residues, a B chain of 32 amino acids, a C region of 104 amino acids, and an A chain of 22 amino acids.

Processing

Cleavage of the signal peptide to generate prorelaxin during transport across the endoplasmic reticulum occurs at the unhindered small amino acid, glycine, consistent with the theory that signal sequences are processed at an amino acid with a small side chain, commonly alanine (Steiner *et al.*, 1980).

Subsequent processing steps are less easy to define. At the carboxyl-terminus of the B chain, the initial cleavage may be at the Leu^{32}–Ser^{33} peptide bond, identical to the main cleavage site of rat relaxin. If so, in pig relaxin the C-terminal leucine residue must be subsequently removed to generate the B31 form which is the major form isolated. Alternatively, the main initial cleavage could be at the Ala^{31}–Leu^{32} bond, with a minor cleavage of the Leu^{32}–Ser^{33} bond. In either situation, the cleavage enzyme must recognize the neutral aliphatic side chains of alanine or leucine and thus may resemble chymotrypsin in its specificity. A chymotryptic-like cleavage at a Leu-Ala-Leu sequence of porcine proinsulin C peptide has been reported (Tager *et al.*, 1973) (Fig. 5).

A similar situation applies at the C region–A chain junction. Inspection of the prorelaxin sequence suggests that the most likely cleavage point would be carboxyl terminal to the four basic residues (Arg-Lys-Lys-Arg) at positions 131–134. This would be identical with the cleavage which generates rat relaxin from its precursor and consistent with the common finding of prohormone processing at clusters

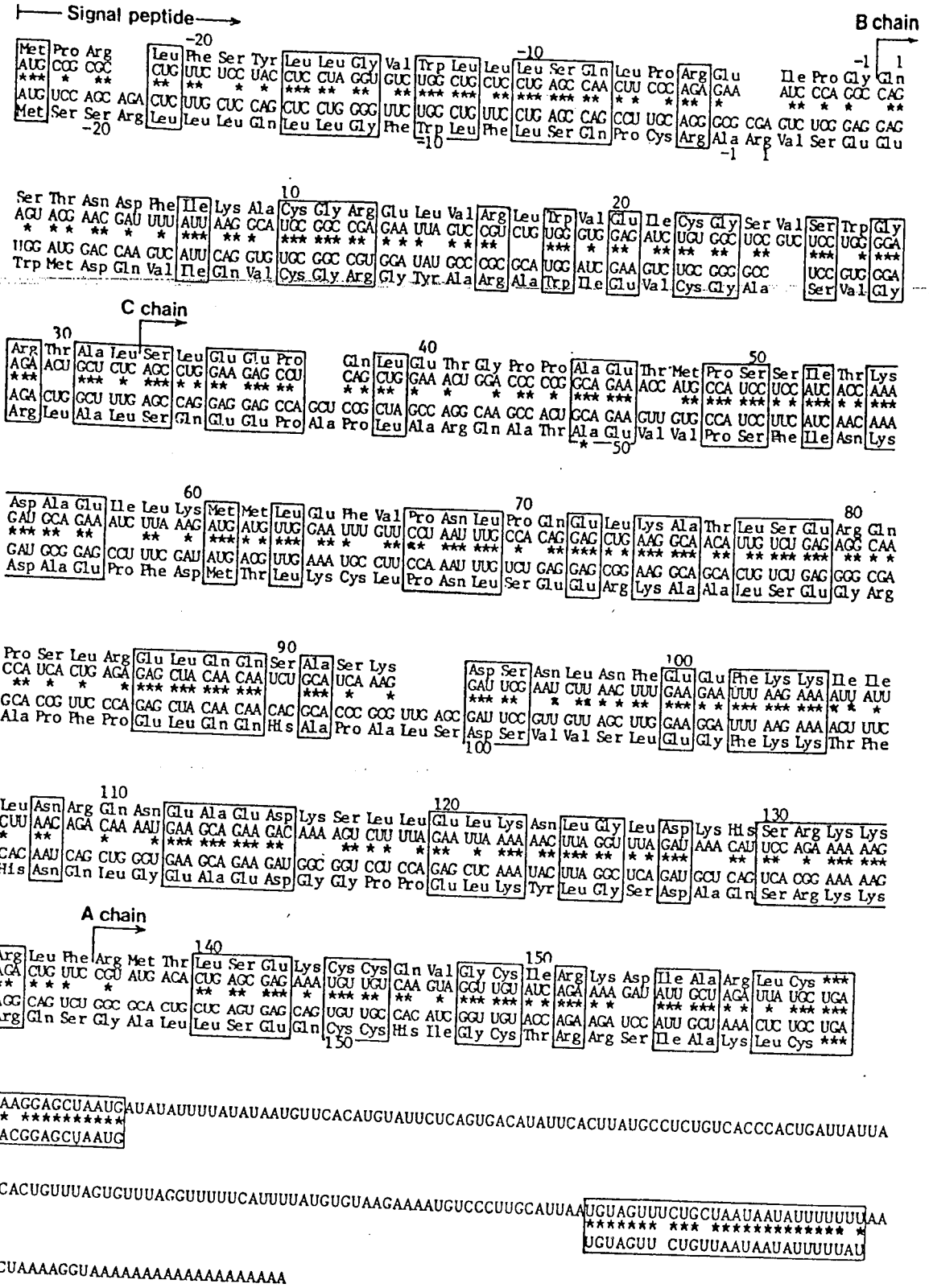


FIG. 4. A comparison of the porcine preprorelaxin amino acid mRNA sequences (top) with the corresponding rat relaxin sequences (bottom). The region of 5′-untranslated sequence was obtained from only a single clone (pRLX2) and is not reported pending confirmatory sequence obtained from another clone. Asterisks indicate nucleotide homology, while the boxed-in areas mark amino acid homologies. Amino acids are numbered from the start of the B chain. The asterisk beneath Ala[49] denotes the putative intron processing site in rat relaxin (Hudson *et al.*, 1981). Little nucleotide homology occurs in the 3′-untranslated region between procine and rat relaxin mRNAs; consequently the rat nucleotide sequence is omitted from all but the boxed-in areas after the termination codon and surrounding the AAUAAUA sequence.

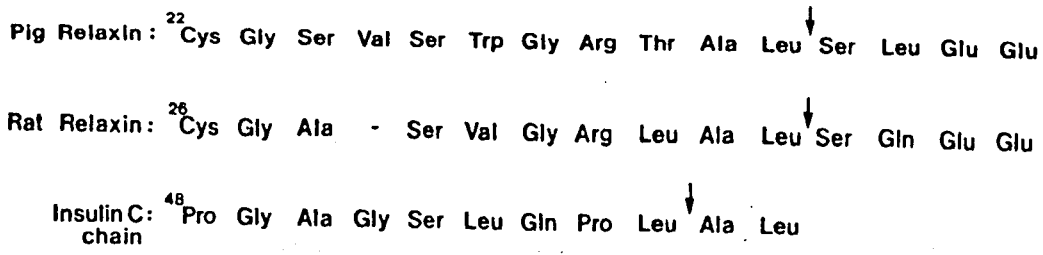


FIG. 5. A comparison of chymotryptic processing sites in the relaxin B chain-C region junction and the insulin C chain (Tager *et al.*, 1973). Cleavage points are marked by an arrow.

of basic residues. However, it would leave an additional dipeptide sequence (Leu–Phe) attached to the amino-terminus of the A chain, which is not present at all in native relaxin as isolated. Such a sequence could be removed rapidly by a DAP I-like enzyme (dipeptidyl aminopeptidase); the exposure of arginine as the new N-terminal residue would prevent further digestion by such as enzyme (McDonald *et al.*, 1977). Again the alternative explanation would be that the initial cleavage is of the Phe^{136}–Arg^{137} bond by a chymotrypsinlike enzyme liberating the relaxin A chain in one step. At present there is insufficient information to decide between these possibilities. However, the processing of rat relaxin must involve at least two enzymes with chymotrypsinlike and trypsinlike specificities respectively (Hudson *et al.*, 1981). Possibly the same applies to pig relaxin. Since chymotrypsin itself rapidly cleaves pig relaxin at several internal bonds (John and Niall, 1980), there must be an additional basis, possibly constraints due to secondary structure, for the specificity of the cleavages occurring during processing of prorelaxin *in vivo*.

If a serine-protease is responsible for the processing of preprorelaxin, an interesting possibility would be the involvement of a toninlike specificity (Thibault and Genest, 1981). Tonin hydrolyses angiotensin I at the Phe–His bond to generate angiotensin II. As shown in Fig. 6, relaxin has some homology with angiotensin I near the C region–A chain processing point. An alternative processing specificity could arise through the evolution of an acid-protease converting enzyme, since rennin (Mercier *et al.*, 1973), renin, and cathepsin D (Hackenthal *et al.*, 1978) all possess hydrophobic specificity in their proteolytic activity.

The limited homology maintained during evolution between insulin and relaxin at key structural points may reflect some constraint on the genetic drift of a tandem repeat of the primordial insulin gene as it evolved a different physiological function.

Homology with rat relaxin

Similar to rat relaxin, the sequence AAUAAUA occurs 19 bases upstream from the start of the polyadenylation site (17 bases upstream in the rat). It is of interest that this sequence in both pig and rat relaxin is slightly different from the AAUAAA signal found in most other eukaryotic mRNAs (Proudfoot and Brownlee, 1976). There are no other areas of significant homology between the 3'-untranslated regions of porcine and rat relaxin cDNAs except for 10 bases following the termination codon and for 25 bases around the AAUAAUA site (Fig. 4). This finding is in general agreement with other eukaryotic gene families in which the 3'-untranslated regions show a higher rate of sequence divergence than the coding regions.

In view of the great divergence between rat and pig relaxin (John *et al.*, 1981), the number of amino acid replacements shown in Fig. 4 is not surprising and represents 50.3% of the prorelaxin primary structure. However, in regions of amino acid homology between rat and pig relaxin, nucleotide sequence tends to be retained, since conserved codon usage is present in 33.3% and silent mutations in only 17.0% of the prorelaxin sequence. Thus, although the amino acid homologies between rat and porcine prorelaxin for the B, C, and A chains are 41.2%, 52%, and 54.5%, respectively, the nucleotide sequence homology is considerably greater at 63.0%, 66.8%, and 64.2%, respectively.

Despite the divergence in amino acid sequence between porcine and rat prorelaxins, the overall percentages of hydrophobic, uncharged polar, acidic, and basic residues remain remarkably similar.

The porcine C region requires the insertion of two gaps, corresponding to a total of three residues, following positions 37 and 93, in order to maximize homology with the C peptide of rat relaxin (Fig. 4). The prorelaxin C chains have the same percentage nucleotide conservation as the A and B chains throughout their entire length, a finding that suggests a functional role for the connecting chain in excess of simply ensuring proper disulfide formation between A and B chains. It is interesting to note that of the 14 glutamic acid residues in the pig prorelaxin C region, 11 are conserved in rat prorelaxin (78.5%), as are all four aspartic acid residues. In addition, the C region has 17 basic amino acid residues, giving an overall charged residue composition of 34%.

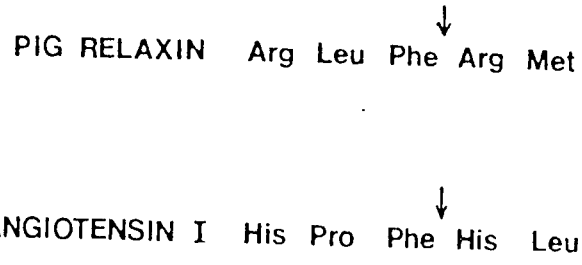


FIG. 6. A comparison of processing at the porcine relaxin C region-A chain junction and the cleavage of angiotensin I by tonin, where a high degree of specificity has been reported (Thibault and Genest, 1981).

This high proportion of acid and basic residues suggests that the C region may either serve to increase the solubility of relaxin intracellularly by increasing the charge exposed to the cytoplasmic environment, or may serve to fold back over the basic relaxin structure to protect it from membrane peptidases. Although no biological activity has been attributed to the C peptide, the possibility of a hormonal role cannot be dismissed.

ACKNOWLEDGMENTS

We thank John Walsh and Mark Birch for their help in obtaining ovaries from pigs in late pregnancy; Christina Fagan for expertise in HPLC purification of synthetic oligonucleotides; and Joanne Hughes for help in M13 sequencing. This work was carried out under NIH/ASCORD containment guidelines for recombinant DNA research. This work was supported by grants from the National Health & Medical Research Council of Australia, the Myer Family Trusts, the Ian Potter Foundation, the Howard Florey Biomedical Foundation (U.S.A.), and by grant HD 11908 (to H.D.N.) from the NIH.

REFERENCES

AVIV, H., and LEDER, P. (1972). Purification of biologically active globin messenger RNA by chromatography on oligothymidylic acid-cellulose. Proc. Natl. Acad. Sci. USA **69**, 1408–1412.

CHIRGWIN, J.M., PRZYBYLA, A.E., MACDONALD, R.J., and RUTTER, W.J. (1979). Isolation of biologically active ribonucleic acid from sources enriched in ribonuclease. Biochemistry **18**, 5294–5299.

GAST, M.J., MERCADO-SIMMEN, R., NIALL, H., and BOIME, I. (1980). Cell-free synthesis of a high molecular weight relaxin-related protein. Ann. N.Y. Acad. Sci. **343**, 148–154.

HACKENTHAL, E., HACKENTHAL, R., and HILGENFELDT, U. (1978). Isorenin, pseudorenin, cathepsin D, and renin: A comparative enzymatic study of angiotensin-forming enzymes. Biochim. Biophys. Acta **522**, 574–588.

HISAW, F.L. (1926). Experimental relaxation of the pubic ligament of the guinea pig. Proc. Soc. Exp. Biol. Med. **23**, 661–663.

HOLMES, D.S., and QUIGLEY, M. (1981). A rapid boiling method for the preparation of bacterial plasmids. Anal. Biochem. **114**, 193–197.

HUDSON, P., HALEY, J., CRONK, M., SHINE, J., and NIALL, H. (1981). Molecular cloning and characterization of cDNA sequences coding for rat relaxin. Nature **291**, 127–131.

ITAKURA, K., BAHL, C.P., KATAGIRI, N., MICHNIEWICZ, J.J., WRIGHTMAN, R.H., and NARANG, S.A. (1973). A modified triester method for the synthesis of deoxypolynucleotides. Can. J. Chem. **51**, 3649-3651.

JAMES, R., NIALL, H., KWOK, S., and BRYANT-GREENWOOD, G. (1977). Primary structure of porcine relaxin: Homology with insulin and related growth factors. Nature **267**, 544–546.

JOHN, M.J., and NIALL, H.D. (1980). Unpublished results.

JOHN, M.J., WALSH, J.R., BORJESSON, B.W., and NIALL, H.D. (1981). Limited sequence homology between porcine and rat relaxin: Implications for physiological studies. Endocrinology **108**, 726–729.

KESSLER, S.W. (1975). Rapid isolation of antigens from cells with a staphylococcal protein A-antibody adsorbant: Parameters of the interaction of antibody-antigen complex with protein A. J. Immunol. **115**, 1617–1624.

MAXAM, A.M., and GILBERT, W. (1977). A new method for sequencing DNA. Proc. Natl. Acad. Sci. USA **74**, 560–564.

MERCIER, J-C., BRIGNON, G., and RIBADEAU-DUMAS B. (1973). Primary structure of bovine kB-casein. Eur. J. Biochem. **35**, 222–235.

MCDONALD, J.K., CALLAHAN, P.X., ELLIS, S., and SMITH, R.E. (1977). In: *Tissue Proteinases.* A.J. Barret and J.T. Dingle, Eds. (North-Holland, Amsterdam) pp. 69–107.

MORRISON, D.A. (1979). In: *Methods in Enzymology.* R. Wu, Ed. (Academic Press, New York) pp. 326–331.

NIALL, H.D., JAMES, R., JOHN, M., WALSH, J., KWOK, S., BRYANT-GREENWOOD, G.D., TREGEAR, G.W., and BRADSHAW, R.A. (1980). *Proceedings of the 15th Midwest Conference on Endocrinology and Metabolism* (Plenum, New York).

NOYES, B.E., MEVARECH, M., STEIN, R., and AGARWAL, K.L. (1979). Detection and partial sequence analysis of gastrin mRNA by using an oligonucleotide probe. Proc. Natl. Acad. Sci. **76**, 1770–1774.

PELHAM, H.R.B., and JACKSON, R.J. (1976). An efficient mRNA-dependent translation system from reticulocyte lysates. Eur. J. Biochem. **67**, 247–256.

PROUDFOOT, N.J., and BROWNLEE, G.G. (1976). 3'-noncoding region sequences in eukaryotic messenger RNA. Nature **263**, 211–214.

ROYCHOUDBURY, R., JAY, E., and WU, R. (1976). Terminal labelling and addition of homopolymer tracts to duplex DNA fragments by terminal deoxynucleotidyl transferase. Nucleic Acid Res. **3**, 863–877.

SANGER, F., COULSON, A.R., BARRELL, B.G., SMITH, A.J.H., and ROE, B.A. (1980). Cloning in single-stranded bacteriophage as an aid to rapid DNA sequencing. J. Mol. Biol. **143**, 161–178.

SCANLON, D. (1981). Unpublished results.

SCHWABE, C., MCDONALD, J.K., and STEINETZ, B.C. (1977). Primary structure of the B-chain of porcine relaxin. Biochem. Biophys. Res. Commun. **75**, 503–510.

SCHWABE, C., STEINETZ, B., WEISS, G., SEGALOFF, A., MCDONALD, J.K., O'BYRNE, E., HOCHMAN, J., CARRIER, B., and GOLDSMITH, L. (1978). Relaxin. Rec. Progr. Horm. Res. **34**, 123–211.

SHERWOOD, O.D., and O'BYRNE, E.M. (1974). Purification and characterization of porcine relaxin. Arch. Biochem. Biophys. **160**, 185–196.

STEINER, D.F., QUINN, P.S., CHAN, S.J., MARSH, J., and TAGER, H.S. (1980). Processing mechanisms in the biosynthesis of proteins. Ann. N.Y. Acad. Sci. **343**, 1–16.

STUDIER, F.W. (1973). Analysis of bacteriophage T7 early RNAs and proteins on slab gels. J. Mol. Biol. **79**, 237–248.

TAGER, H.S., EMDIN, S.O., CLARK, J.L., and STEINER, D.F. (1973). Studies on the conversion of proinsulin to insulin. J. Biol. Chem. **248**, 3476–3482.

TANAKA, T., and WEISBLUM, B. (1975). Construction of a colicin E1-R factor composite plasmid in vitro: Means for amplification of deoxyribonucleic acid. J. Bacteriol. **121**, 354–362.

THAYER, R.E. (1979). An improved method for detecting foreign DNA in plasmids of *Escherichia coli.* Anal. Biochem. **98**, 60–63.

THIBAULT, G., and GENEST, J. (1981). Tonin, an esteroprotease from rat submaxillary glands. biochim. Biophys. Acta **660**, 23–29.

ULLRICH, A., SHINE, J., CHIRGWIN, J., PICTET, R., TISCHER, E., RUTTER, W.J., and GOODMAN, H.M. (1977). Rat insulin genes: Construction of plasmids containing the coding sequences. Science **196**, 1313–1319.

VOGT, V.M. (1973). Purification and further properties of single-strand-specific nuclease from *Aspergillus oryzae*. Eur. J. Biochem. 33, 192–200.

WALSH, J.R., and NIALL, H.D. (1980). Use of an octadecyl-silica purification method minimizes proteolysis during isolation of porcine and rat relaxins. Endocrinology 107, 1258–1260.

WICKERS, M.P., BUELL, G.N., and SCHIMKE, R.T. (1978). Synthesis of double-stranded DNA complementary to lysozyme, ovomucoid, and ovalbumin mRNAs. J. Biol. Chem. 253, 2483–2495.

Address reprint requests to:
Dr. H. Niall
Howard Florey Institute of
Experimental Physiology and Medicine
University of Melbourne
Parkville, Victoria, Australia 3052

Received for publication December 22, 1981.

Office européen des brevets
DG 1

European Patent Office
DG 1

Europäisches Patentamt
GD 1

P.B. 5818 Patentlaan, 2
2280 HV RIJSWIJK (ZH)
Pays-Bas / Netherlands / Niederlande

Telex 31651-epo.nl
(070) 90 67 89
BREVPATENT

National Institute of General Medical Sciences
Department of Health and Human Services
Bethesda, MD 20214
U.S.A.

Rijswijk: 4th November 1983.

Dear Sirs,

We kindley ask you to inform us about the exact date of publication of an article in your magazine:

DNA, Vol. 1 (1982) No. 2 pages 155-162
J. Haley, P. Hudson, D. Scanlon, John M. Cronk, J. Shine, G. Tregear, H. Niall: "Porcine relaxin: molecular cloning and cDNA Structure."

Date of publication ...August 24, 1982....

In your convenience, please fill in the publication date on the enclosed copy and sign it before returning to our address.

Thanking you in advance, we remain.

(Mrs Golligani)
Mr Dekeirel
regu
[illegible] JAN. [illegible]

Yours sincerely,

K. Veen (library)

Bernadette L. Santiago
Mary Ann Liebert, Inc. Publishers
157 E. 86th Street
New York, NY 10028
1 1 S 17

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 101 309**
B1

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **16.01.91**

(51) Int. Cl.[5]: **C 12 N 15/16**, C 07 K 13/00, C 07 K 7/00

(21) Application number: **83304662.6**

(22) Date of filing: **11.08.83**

(60) **Divisional application 88104503 filed on 21.03.88.**

(54) **Molecular cloning and characterization of a gene sequence coding for human relaxin.**

(30) Priority: **12.08.82 AU 5352/82**

(43) Date of publication of application:
22.02.84 Bulletin 84/08

(45) Publication of the grant of the patent:
16.01.91 Bulletin 91/03

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

(56) References cited:
EP-A-0 086 649 **DE-A-3 102 487**

Nature, vol.291, 1981, pp127-131; Genetic Engineering, Commercial Opportunities in Australia, Proceedings of a Symposium in Sydney, 18-20 Nov 1981, pp135-138, Australian Government Public Service

NATURE, vol. 301, no. 5901 February 17, 1983, Macmillan Journals Ltd. Basingstoke, GB, P Hudson et al.: "Structure of a genomic clone encoding biologically active human relaxin", pages 628-631

(73) Proprietor: **HOWARD FLOREY INSTITUTE OF EXPERIMENTAL PHYSIOLOGY AND MEDICINE**
c/o University of Melbourne
Parkville Victoria (AU)

(72) Inventor: **Hudson, Peter John**
1 Sefton Street, Bulleen
Victoria (AU)
Inventor: **Shine, John**
107 Barnett Close, Swinger Hill
Australian Capital Territory (AU)
Inventor: **Niall, Hugh David**
3 Bendigo Avenue, Elwood
Victoria (AU)
Inventor: **Tregear, Geoffrey William**
62 Hawthorn Grove, Hawthorn
Victoria (AU)

(74) Representative: **Brown, John David et al**
FORRESTER & BOEHMERT Widenmayerstrasse 4/I
D-8000 München 22 (DE)

Courier Press, Leamington Spa, England.

EP 0 101 309 B1

(56) References cited:

TELEGEN TECHNICAL FEATURE 82000533, Abstract 31808, 1982 Environment Information Center New York, US, H NIALL: "Hormones and genetic engineering" paper presented at the genetic engineering symposium in Sydney, November 18-20, 1981

DNA, vol. 1, no. 2, 1982, Mary Ann Liebert Inc. New York, US, J HALEY et al.: "Porcine Relaxin: Molecular Cloning and cDNA Structure", pages 155-162

NATURE, vol. 267, 1977, pages 544-546, Macmillan Journals Ltd. Basingstoke, GB; R JAMES et al.: "Primary structure of porcine relaxin: homology with insulin and related growth factors"

Description

This invention relates to the molecular cloning and characterization of the gene sequence coding for human relaxin. The invention is also concerned with recombinant DNA techniques for the preparation of human relaxin, prorelaxin and preprorelaxin.

More specifically, this invention relates to an isolated and purified ("cloned") human gene coding for prorelaxin, preprorelaxin, and the A and/or B and/or C peptide chains of human relaxin, methods for isolating and purifying the genes and methods for transferring the genes to and replicating the genes in a host cell. The cloned genes are expressed by the host cell when fused with a host-expressable prokaryotic or eukaryotic gene. The genes are thus useful in the production of human relaxin for therapeutic purposes.

The invention also relates to the peptides human relaxin, prorelaxin and preprorelaxin, to the individual peptide chains which comprise these sequences and to modified forms of these peptides.

The invention further relates to modified genes coding for the individual relaxin chains and for the above-mentioned modified forms.

Note: References referred to by number used in the following description are collected at the end of the description.

Pioneeing work by Hisaw (1) suggested an important role for the peptide homone relaxin in mammals through its effects in dilating the cervix and softening the pubic symphysis, thus facilitating the birth process. Relaxin is synthesized and stored in the corpora lutea of ovaries during pregnancy and is released into the blood stream prior to parturition. The availability of ovaries has enabled the isolation and amino acid sequence determination of relaxin from pig (2, 3) rat (4) and shark (5). The biologically active hormone consists of two peptide chains (known as the A and B chains) held together by disulphide bonds, two inter-chain and one intra-chain. The structure thus closely resembles insulin in the disposition of disulphide bonds which has led to speculation of a common ancestral gene for these hormones (2, 3).

A process for the preparation of human relaxin from chorionic membrane has been disclosed in DE—A—3102487.

Recombinant DNA techniques have been applied to the isolation of cDNA clones for both rat and porcine relaxins (6), (7), see also European Patent Application No. 0086649. Synthetic undecamer nucleotides, prepared on the basis of amino acid sequence information, were used as primers for the synthesis of cDNA probes greatly enriched in relaxin cDNA sequences which identified relaxin cDNA clones in libraries derived from ovarian tissue. The relaxin structural gene was found to code for a single chain precursor which resembles preproinsulin in the overall configuration, i.e., signal peptide/B chain/C peptide/A chain.

Pig and rat preprorelaxins contain an unexpectedly large connecting peptide of 105 and 104 residues respectively in comparison to rat insulin with a C peptide of about 30 residues. A high degree of sequence homology in the C-peptide of rat and pig relaxin suggests a role beyond simply ensuring the correct disulphide bond formation of the A and B chains. We predicted that structural constraints on sequence divergence applying during evolution would have resulted in the C-peptide region having a similarly high degree of sequence homology in the human relaxin gene. Accordingly, as described hereinafter, we have used probes based on the C-peptide region of procine rather than rat relaxin in the selection of the human relaxin gene because the accumulation of protein sequence data indicated that human proteins are in general less divergent from porcine than from rat proteins (8).

Although it has been the long term goal of several groups to determine the structure of human relaxin and so establish a route to clinical intervention in cases of difficult labour, the limited availability of human ovaries during pregnancy has prevented direct amino acid sequence determination. Our approach was to screen directly for the human relaxin gene in a genomic library using a region of the porcine relaxin cDNA as a probe. This approach resulted in the successful identification of genomic clone from which the structure of the entire coding region of preprorelaxin has been determined.

It is now believed that either or both the presently-described gene which we have designated "H1" and the "H2" gene described in our copending European application No. EP—A—0112149 are expressed in human reproductive tissue, for example ovary and placenta, and/or other tissues including but not limited to gut, brain and skin, since both genes express peptides with relaxin-like activity.

The corpora lutea of the ovary as well as decidual and placental tissues are the most likely sites for expresson of relaxin-related genes. However, in view of the wide distribution of many peptide hormones it is highly likely that the relaxin gene is also expressed in non-reproductive tissues, including brain and the gastrointestinal tract. Relaxin has the general properties of a growth factor and is capable of altering the natue of connective tissue and influencing smooth muscle contraction. We believe that one or both of the gene structures described in this and the copending patent application EP—A—0112149 to be widely distributed in the body. We suggest that the relaxin peptides expressed from these genes will play an important physiological role in addition to their well documented hormonal function during reproduction.

The following abbreviations are used in this description.

H1 — the relaxin gene described herein, being deduced from a genomic clone.

H2 — the relaxin gene described in copending Application No. EP—A—0112149 being deduced from a cDNA clone.

DNA — deoxyribonucleic acid
RNA — ribonucleic acid
cDNA — complementary DNA (enzymatically synthesized from an mRNA sequence)
mRNA — messenger RNA

A — Adenine
T — Thymine
G — Guanine
C — Cytosine
U — Uracil

The coding relationships between nucleotide sequence in DNA and amino acid sequence in protein are collectively known as the genetic code, which is set out below.

First position (5'end)	Second position U	C	A	G	Third position (3' end)
U	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	Stop	Stop	A
	Leu	Ser	Stop	Trp	G
C	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu	Pro	Gln	Arg	G
A	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val	Ala	Glu	Gly	G

The abbreviations used for the amino acids in the table are identified as follows.

Phenylalanine	(Phe)	Histidine	(His)
Leucine	(Leu)	Glutamine	(Gln)
Isoleucine	(Ile)	Asparagine	(Asn)
Methionine	(Met)	Lysine	(Lys)
Valine	(Val)	Aspartic acid	(Asp)
Serine	(Ser)	Glutamic acid	(Glu)
Proline	(Pro)	Cysteine	(Cys)
Threonine	(Thr)	Tryptophan	(Try)
Alanine	(Ala)	Arginine	(Arg)
Tyrosine	(Tyr)	Glycine	(Gly)

Each 3-letter codon represented in the table, e.g., AUG, CAU (otherwise known as a deoxynucleotide triplet or nucleotide triplet) corresponds to a trinucleotide of mRNA, having a 5'-end on the left and a 3'-end

on the right. The letters stand for the purine or pyrimidine bases forming the nucleotide sequence. All DNA sequences given herein are those of the strand whose sequence corresponds to the mRNA sequence, with thymine (T) substituted for uracil (U).

In the following discussion reference will be made to the accompanying drawings in which:

Figure 1 is an abbreviated restriction enzyme map of the two genomic clones mentioned below;

Figure 2 shows how to align figures 2a and 2b which when aligned give the mRNA sequence of the coding region of the human relaxin gene and the amino-acid sequence of human preprorelaxin; and

Figure 3 shows a comparison of the human preprorelaxin and mRNA sequences with the corresponding sequences for porcine preprorelaxin.

The original source of genetic material was a library of human genomic clones. Screening of this library using pig relaxin cDNA probes yielded two clones containing coding sequences of human relaxin.

The mRNA sequence shown in Figures 2 and 3, was determined by the methods described hereinafter. It will be seen that a single intron of 3.4kb interrupts the coding region of the connecting (C) peptide. The structure of human preprorelaxin was deduced from the genomic sequence by comparison with the homologous structures of pig and rat relaxin. Confirmation of the A and B peptide chain structures has been provided by synthesis and chain recombination *in vitro* which produces a material which is biologically active in the uterine contraction assay.

The mode of *in vitro* processing of the preprorelaxin is not yet fully known but by analogy with pig relaxin cleavage of the signal peptide would be expected to occur at the Ala^{-1}-Lys^{1} bond. Similarly excision of the C peptide is predicted to occur at Leu^{32}-Ser^{33} and Arg^{136}-Arg^{137}, thus giving the B and A chains of respectively 32 and 24 residues.

As noted in our studies on pig relaxin, thee are core sequences in the pig relaxin B and A chains which contain all the essential elements for biological activity. Our synthetic studies on the human relaxin chain show similar results, as set out in more detail hereinafter.

According to one aspect of the present invention, there is provided a gene for the expression of human preprorelaxin.

More specifically, this aspect of the invention provides a double-stranded DNA fragment for the expression of human preprorelaxin, which comprises a coding strand and a complementary strand corresponding to the complete mRNA (codons −25 to 160) sequence shown in Figure 2 of the accompanying drawings.

The invention also includes any sub-unit of the preprorelaxin gene sequence described herein, or any equivalent of the said sequence or sub-unit. Among the sub-units to be included by this statement are genes which exclude non-coding regions, such as those shown in Figure 3, genes containing the individual structural genes coding for the signal peptide chain and the A, B and C chains of human preprorelaxin (see Figure 3) and any combinations of these chains, e.g., the genes for expressing the A and B peptide chains, separately or as prorelaxin (with the C chain).

Thus according to another aspect of the present invention, there is provided a gene for the expression of human prorelaxin.

More specifically, this aspect of the invention provides a double-stranded DNA fragment for the expression of human prorelaxin, which comprises a coding strand and a complementary strand corresponding to the codons numbered as 1 to 160 of the mRNA sequence shown in Figure 2 of the accompanying drawings.

According to a further aspect of the present invention, there are provided genes for the separate expression of the A, B and C chains of human relaxin or any combination of two or more of the said chains.

More specifically, this aspect of the invention provides double-stranded DNA fragments for the separate expression of the A and/or B and/or C chains of human relaxin, which comprise a coding strand and a complementary strand corresponding to the codons numbered 1 to 32, 33 to 136 and 137 to 160 of the mRNA sequence shown in Figure 2 of the accompanying drawings.

The genes described above in addition to the codons specified may also include the appropriate "start" and "stop" codons, i.e., AUG and UGA respectively (codons −26 and 161 in Figure 2).

Those skilled in the art will appreciate that polymorphic forms of the geners may exist. Such forms are included in the present invention.

The invention further includes the complements of the above sequences, sub-units or equivalents, and the corresponding RNA sequences, sub-units or equivalents.

According to another aspect of the present invention there is provided a DNA transfer vector comprising the deoxynucleotide sequences corresponding to the genes defined above.

As shown above, the genetic code contains redundancies, that is certain amino acids are coded for by more than one codon. Thus the invention includes deoxynucleotide sequences in which the codons depicted in the drawings, or their cDNA equivalents are replaced by other codons which code for the same amino-acid.

Furthermore, as already indicated above, peptides with relaxin activity may be produced which differ from the B and/or A chain structures of natural relaxin. Such differences may involve deletion of one or more amino acids and/or addition of further amino acids and/or substitution of different amino acids in the natural chains.

Thus the invention also includes genes and DNA transfer vectors as described above wherein one or

more of the natural codons are deleted and/or are replaced by codons which code for amino acids other than that coded by the natural codon, and/or further codons are added to the natural sequence.

The transfer vectors of the invention may also include *inter alia*, genetic information which ensures their replication when transferred to a host cell. Such cells may include, for example, the cells of prokaryotic microorganisms, such as bacteria, yeasts and moulds, and also eucaryotic cells, including mammalian cells and cells lines.

Examples of transfer vectors commonly used in bacterial genetics are plasmids and the DNA of certain bacteriophages. Both phage DNA and bacterial plasmids have been used as the transfer vectors in the present work. It will be understoof however, that other types of transfer vectors may be employed. The general techniques of forming such transfer vectors and transforming them into microorganisms are well known in the art.

The invention also includes a prokaryotic or eukaryotic cell transformed by any of the transfer vectors described above.

One preferred microorganism is the very familiar *Escherichia coli,* but any other suitable microorganism may be used.

According to a still further aspect of the present invention, there is provided a process for making a DNA transfer vector for use in maintaining and replicating a deoxynucleotide sequence coding for human preprorelaxin, characterised by ligating a deoxynucleotide sequence coding for human preprorelaxin with a DNA molecule prepared by cleaving a transfer vector with a restriction enzyme.

DNA transfer vectors for use in maintaining and replicating deoxynucleotide sequences coding for human prorelaxin and for the A and B chains of human relaxin may be similarly prepared from the appropriate deoxynucleotides.

The A and B peptide chains, and also prorelaxin and preprorelaxin may be prepared by the usual process of gene expression, that is by growing cells containing the appropriate transformed transfer vector and isolating and purifying the required peptide(s) produced by the cells.

Thus, the invention further includes a process for making a fusion protein comprising the amino acid sequence of human preprorelaxin as its C-terminal sequence and a portion of a prokaryotic or eukaryotic protein as its N-terminal sequence, characterised by incubating a cell culture transformed by an expression transfer vector comprising a deoxynucleotide sequence coding for human preprorelaxin, prepared in accordance with the process described above.

Fusion proteins comprising the amino acid sequences for human prorelaxin and the A and B chains of human relaxin may be similarly prepared.

The fusion peptide products thus produced will be in the form of a fusion protein in which the desired peptide is linked with a portion of a prokaryotic or eukaryotic protein characteristic of the host cell. Such fusion proteins also form a part of this invention.

The invention also includes a process for synthesizing human prorelaxin comprising the A and B peptides separated from each other by a C peptide, characterised by incubating a culture of cells, transformed by an expression transfer vector comprising a deoxynucleotide sequence coding for said human prorelaxin, prepared as described above, under conditions suitable for expression of said sequence coding for human prorelaxin, and purifying human prorelaxin from the lysate or culture medium of said cells.

The peptide of interest can be recovered from the fusion product by any suitable known cleavage procedure.

As already indicated above the transfer vector may be modified by codon substitution/deletion/addition and such modifications will give rise to modified fusion peptides. In this way appropriate modifications may be made to facilitate the cleavage of the fusion peptides, for example, at the junction of B/C or C/A chains or to modify the peptide chain behaviour during subsequent chemical or biological processing.

As indicated above, the invention also provides human relaxin, prorelaxin and preprorelaxin.

Relaxin may be prepared by direct combination of the separate A and B chains by any of the procedures currently known and used for the preparation of insulin.

Also in a similar manner to insulin, relaxin may be prepared from prorelaxin by oxidizing or otherwise converting the sulfhydryl groups on the A and B peptides of relaxin, prepared as described herein, to form disulfide crosslinks between said A and B peptides, and then excising the C peptides, for example, by an enzyme-catalyzed hydrolysis specific for the bonds joining the C peptide to the A and B peptides.

The European patent application EP—A—287820, which is a divisional application of the present application, provides a method for the synthesis of human relaxin which comprises combining the A and B chains of relaxin (in their full-length, shortened or modified forms) by methods known *per se* for combination of A and B chains of human insulin.

One such method comprises reducing a mixture of the S-sulphonated A and B chains and then allowing the mixture to oxidize in air.

We have also found that the efficiency of the above procedure is improved when one or both of the A and B chains is in the form of an S-thioethyl-cys derivative rather than the S-sulpho form.

In our Australian Patent Application No. 15413/83 (PF 4385/82) we also showed that one or both of the A and B chains of relaxin can be shortened at the amino and/or carboxy terminii without significant loss of

biological activity and with improved combination yields. These techniques apply equally to the preparation of human relaxin.

The European patent application EP—A—287820 quoted above provides a human relaxin analogue consisting essentially of shortened and/or modified forms of the natural B and/or A peptide chains and also provides a method for producing a human relaxin analogue which comprises the step of forming the shortened and/or modified B and/or A peptide chains and combining them by any of the methods described above.

Our investigations with both pig and human relaxin show that relaxin activity may be present with A chains as short as A(10—24) and B chains as short as B(10—22) although the expected practical minima are respectively A(4—24) and B(4—23).

In general, the A chain can be varied from A(1—24) to A(10—24) and B chain from B(1—32) to B(10—22).

The preferred combinations are derived from:

	A		B
	(1—24)		(1—23)
any of	(2—24)	with any of	(up to)
	(3—24)		(1—32)

Modifications of the B and/or A chains, in accordance with the present invention may involve either "genetic" modification, as described above or chemical modification of the B and/or A chains (in either full-length or shortened form) prior to combination by the methods of the invention. Two types of modification may be employed, either singly or in combination.

The first type involves the modification of one or more of the amino-acids which occur in the natural or shortened B and/or A chains. Such modification will generally involve protection of active groups on one or more of the amino-acids by methods known *per se*, and the protecting groups may, if desired, be removed after combination of the (modified) A and B chains.

Examples of this type of modification include the acetylation, formylation or similar protection of free amino groups, including the N-terminal, amidation of C-terminal groups, or the formation of esters of hydroxyl or carboxylic groups. The formyl group is a typical example of a readily-removable protecting group.

The second type of modification includes replacement of one or more of the natural amino-acids in the B and/or A chains with a different amino acid (including the D-form of a natural amino-acid). This general type of modification may also involve the deletion of a natural amino-acid from the chain or the addition of one or more extra amino-acids to the chain.

The purpose of such modifications is to enhance the combination yields of the A and B chains, while maintaining the activity of the product, i.e., relaxin or an analogue thereof, or to enhance or modify the activity of the product for a given combination yield. Such modification may extend to the production of synthetic analogues which have relaxin-blocking or -antagonistic effects.

A specific example of the first type of modification is the modification of the trytophan (Trp) residue at B2 by addition of a formyl group.

Examples of the second type of modification are replacement of the Met moiety at B24 with norleucine (Nle), valine (Val), alanine (Ala), glycine (Gly), serine (Ser) or homoserine (HomoSer).

The invention in this aspect also includes human relaxin analogues formed from natural or shortened B and/or A chains modified in accordance with the invention as described above.

The A and B peptide chains, and also prorelaxin and preprorelaxin may be prepared by the usual process of gene expression, that is by growing a microorganism containing the appropriate transformed transfer vector and isolating and purifying the required peptide(s) produced by the microorganism.

The peptide products thus produced may be in the form of a fusion protein in which the desired peptide is linked with a portion of a prokaryotic protein.

The invention is further described and illustrated by the following description of the experimental procedures used and the results obtained thereby.

A. Experimental Procedures

(i) Bacterial and Phage Strains

E. coli RR1 was used as the bacterial host for recombinant plasmids (pBR322) containing porcine relaxin cDNA insertions as described previously (7).

The library of human genomic clones was kindly provided by T. Maniatis. Genomic DNA fragments of about 15—20 kb, from the partial Hae 111/Alu 1 fragmentation of the human DNA (9), were cloned by liners into the lambda phase vector Charon 4A (10) and propagated in *E. coli* LE392 cells.

Phage DNA (after clone selection) was prepared following lysis of *E. coli* DP50supF cells in 1 litre cultures (10).

Small DNA fragments (from fragmentation of phage DNA) were subcloned for sequence analysis into the M13 bacteriophage vectors mp7.1, mp8 and mp9 (kindly provided by Dr. J. Messing) and transformed into *E. coi* JM101 cells.

(ii) Preparation of hybridization probes (porcine DNA)

Radiolabelled probes were prepared by primed synthesis on various DNA fragments using denatured random primers (3 or 4 bases) of calf thymus DNA (11). The porcine DNA template (100—200 ng) was denatured with the random primers (1 µg) by boiling in 20 µl of H_2O for 2 minutes. Synthesis was initiated by the addition of a 30 µl reaction mixture containing 50mM Tris-HCl pH 8.0, 50mM NaCl, 1mM DTT, 10mM $MgCl_2$, 5 units of *E. coli* DNA Polymerase 1, 500 M each of dCTP, dGTP, dTTP and 0.3 µM α-[^{32}P]-dATP (approx. 3000 Ci/mmol, Amersham). After incubation at 37°C for 30 minutes the reaction was terminated by dilution into 300 µl of a buffer containing 0.3M NaCl, 10mM Tris-HCl, pH 8.0, 1mM EDTA and passed through a Sephadex—G50 column, (1 cm × 5 cm) in the same buffer. The radiolabelled probe was collected from the peak fractions at void volume and precipitated with 2 volumes of ethanol at −20°C for 2 hours using tRNA (10 µg) as carrier.

(iii) Screening procedures

Lambda phage (λ) containing genomic DNA fragments were grown on soft agar at about 10^5 phage/13 cm diam. plate and transferred to nitrocellulose filters (Schleicher & Schull BA85) as described by Benton and Davis (12). Filters were hybridized with the radiolabelled probe at 40°C for 18 hours in modified Denhart's solution (13) containing 5 × SSC and 25% formamide. Filters were washed in 2 × SSC at 30° for 1 hour before exposing to x-ray film (Kodak XS—5) for 24 hours. Regions of the plate which exhibited positive hybridization were subcultured and rescreened successively until single positive plaques could be selected. Phage were harvested after lysis of 1 litre cultures of *E. coli* I DP50supF cells and DNA prepared by the methods described by Maniatis (10) and Yamamoto and Alberts (14).

(iv) DNA Sequence Analysis

Restriction fragments of the selected recombinant phage were subcloned directly into the Eco R1, Pst 1 or Sma 1 site of phage M13mp8. Ligations were carried out in 20 µl reactions containing 10mM Tris-HCl pH 8.0, 10mM $MgCl_2$, 1mM DTT, 1mM ATP, 1 unit of T4 DNA ligase, DNA (100 ng) and the M13 phage vector (50 ng). After incubation at 40°C overnight recombinant DNA was transformed into *E. coli* JM101 cells (15). Plaques containing the coding region were selected by a similar technique as described for the genomic screens above, except the M13 phage were plated at lower density (10^3 phage/9 cm diam. plate). Positive plaques were grown for a preparative yield of either single stranded template or replicative double stranded (rf) form (15). Single stranded templates were sequenced directly by the method of Sanger et al. (16) using either an M13-specific primer (Collaborative Research) or synthetic primers complementary to various sequences in the coding region. Complete sequence analysis of the subclones was obtained by cleavage of the rf form at several sites with various restriction enzymes followed by subcloning into M13 by blunt end ligation (15) or by directly end-labelling fragments and sequencing by the method of Maxam and Gilbert (17). DNA sequence was analysed and compared to the porcine and rat relaxin sequences using computer programmes (18).

B. Results

In the following discussion, reference will be made to the drawings.

Figure 1 shows an abbreviated restriction enzyme map of the genomic clones.

Sizes are given in kilobase-pairs (kb) and cleavage sites are designatd EcoR1 (R), Pst 1(P) and Hpa 11(H). The genomic clone λH5 terminates at an Eco R1 linker attached to the Alu 1 site in the C peptide (exon II) (A* in Figure 1). The definitive nucleotide sequence over the coding region was compiled from the genomic clone λH7 by subcloning Eco R1 and Pst 1 fragments into M13mp8 and then either:

(1) direct sequencing shown by dashed lines in Figure 1 (- - - -) on M13 templates

(2) direct sequencing using synthetic nucleotide primers shown by dotted lines (. . . .)

(3) end-labelling DNA fragments and sequencing shown by solid lines (——) by chemical degradation.

The primers used for sequencing were

a: 5'TTCGCAATAGGCA and b: 5'GCACAATTAGCT.

Figure 2 shows the coding region of the human relaxin gene.

A comparison of the human preprorelaxin amino acid and mRNA sequence (upper) with the corresponding porcine relaxin sequence (lower) is shown in Figure 3. The sequences have been aligned to maximize homology with nucleotide identities being indicated by asterisks and amino acid homologies by boxed-in areas. Amino acids are numbered from the start of the B-chain. The intron sequence at the exon/intron/exon boundaries is presented in lower case DNA notation.

(i) Isolation and characterization of genomic clones

Human genomic clones were identified by screening the library with probes made from a short (150bp) fragment of the procine relaxin cDNA clone corresponding to amino acids 45—95 in the C-peptide (7) as set out in Figure 3 of the accompanying drawings. This fragment was excised from the clone by digestion with Hpa II and HinfI and corresponded to the region of maximum homology (71% at the nucleotide level) between rat and porcine relaxin sequences. From the genomic clone bank, two strongly positive phage designated λH5 and λH7 were isolated. These positive clones were further characterized by restriction enzyme analysis using as probes two separate fragments of porcine relaxin cDNA specific for the 5' and 3' exon regions respectively (hereinafter called "exon I" and "exon II"). The two fragments were generated by

cleavage of the porcine relaxin cDNA clone at a single Hpa II site which corresponds (within a few bases) to an intron site in the homologous rat relaxin gene (6). Southern blot analysis of the λH5 and λH7 clones revealed that the coding region of the human relaxin gene is interrupted by a single intron of 3.4 kb (see Figure 1).

(ii) Sequence Analysis of the Genomic Clones

The strategy used was to subclone complete restriction digests of λH5 and λH7 into M13 vectors and then screen using porcine relaxin probes specific for exons I and II. The positive subclones were sequenced by a combination of techniques described in the methods section (A(iv) above).

The exon II region of the λH7 clone was contained in a 2.0 kb EcoR1 fragment beginning at an Eco R1 site in the C-peptide and continuing through the entire coding sequence of the A chain to the termination codon (see Fig. 1). Sequencing of this fragment was aided considerably by the synthesis of nucleotide primers specific for regions around the A chain which were used to prime directly on the M13 template containing the entire 2.0 kb fragment. The subcloned Eco R1 fragment containing the remaining 53 bp of the C-peptide in exon II could not be identified with the porcine cDNA as a probe. The sequence over this region was obtained by a subcloned Pst 1 fragment from λH7 which contained the entire exon II region.

Sequencing the exon II region of λH5 revealed an extremely short 70 bp fragment beginning at the same Eco R1 site in the C-peptide as λH7 (see Fig. 1) but terminating with an Eco R1 linker which had been attached to an Alu 1 site in the original genomic DNA during the generation of the genomic library. Thus λH5 was designated an incomplete clone of the relaxin gene and was not analysed further.

Sequence analysis of the exon I region was slightly complicated by an Eco R1 site in the signal peptide which necessitated the independent sequencing of two Eco R1 fragment subclones. The overlap over the Eco R1 site was supported by the identification of a Alu I subclone from λH7 which contained the overlapping sequence.

C. Synthesis of a modified human relaxin (hRLX) A(1—24) — B(1—25)

(i) Synthesis of human relaxin A-chain, hRLX A(1—24)

The amino acid sequence corresponding to residues 1 to 24 of the human relaxin A-chain, deduced as described above from the nucleotide sequence of the genomic clone, was synthesized by the solid-phase procedure according to the general principles described by Merrifield (e.g. Barany, G. and Merrifield, R. B. In "The Peptides". Ed. E. Gross & J. Meienhofer, Academic Press, N.Y., pp. 1—284, 1980).

N-α-tertiarybutyloxycarbonyl*-4-methylbenzyl-L-cysteine (*hereinafter "BOC") was coupled to a 1% crosslinked polystyrene resin *via* the phenylacetamidomethyl (PAM) linkage to a level of 0.30 mmole/gm using the method of Tam et al., (Synthesis *12*, 955—957, 1979). The BOC-L-CYS-PAM (8.0 gm) was transferred to the reaction vessel of a Beckman Model 990 Peptide Synthesizer and the amino acid sequence from residues 23 through to 1 was assembled by the stepwise addition of each suitably protected amino acid. The amino terminal BOC protecting group of each amino acid was removed by treatment of the resin with 35% trifluoroacetic acid in methylene chloride for 30 minutes followed by neutralizaton with 5% diisopropylethylamine in methylene chloride for 15 minutes. After each treatment the resin was washed thoroughly with methylene chloride. The next amino acid in the sequence (suitably protected at the α-amino with the BOC group and where necessary with the side-chain functional group appropriately protected) was coupled to the resin using dicyclohexylcarbodiimide (DCC). The resin was stirred with the amino acid in methylene chloride for 10 minutes prior to the introduction of the DCC which was also dissolved in methylene chloride. A 2.5 molar excess (6.0 mmole) of amino acid and DCC was used for each coupling. After stirring for 1 hour a sample of the resin was removed from the reaction mixture and tested for the presence of free amino groups using the ninhydrin procedure of Kaiser et al. (Anal. Biochem., *34*, 595—598, 1970). If the ninhydrin test was negative indicating complete coupling the reaction cycle was continued with BOC deprotection, neutralization and coupling of the next amino aid. For a positive ninhydrin test the coupling reaction was repeated with further amino acid and DCC.

Amino acids with side-chain functional groups were used as the following protected derivatives: N-α-BOC-2,6-dichlorobenzyl-L-tyrosine, N-α-BOC-ε-chlorobenzylcarbonyl-L-lysine; N-α-BOC-L-serine O-benzyl ether; N-α-amyloxycarbonyl-N^G-tosyl-L-arginine; N-α-BOC-L-threonine O-benzyl ether; N-α-BOC-S-ethyl mercapto-L-cysteine (for CYS at A-chain sequence position 15, 11 and 10); N-α-BOC-L-glutamic acid-γ-benzyl ester.

Following the assembly of the 1—24 peptide sequence, the final BOC group on the amino terminal arginine was removed using the deprotection neutralization cycle and the peptide-resin dried in vacuo (wt of peptide resin 17.0 gm). A portion of the peptide-resin (2 gm) was treated with anhydrous hydrogen fluoride in the presence of anisole (2 ml) at 0°C for 30 minutes. The total time for contact of the resin-peptide with hydrogen fluoride (HF) was kept to a minimum (not more than 70 minutes) by rapid removal of the HF under oil-pump vacuum. The resin-peptide was then washed several times with ethyl acetate to remove excess anisole, the peptide extracted into 1M acetic acid and the solution lyophilized. The yield of crude peptide, (with the cysteines at positions 10, 11 and 15 still protected as the S-thioethyl derivative) was 440 mg. Initial purification of the crude peptide was by gel-filtration on Biogel P10 in 0.1M acetic acid. The fractions representing the major peak from this column, which eluted at a position corresponding to a molecular weight of approximately 3000, were collected and lyophilized. Amino acid analysis of a sample

of this peptide indicated that all the amino acids of the 1—24 sequence were present in the correct ratio.

Further purification of the [S-thioethyl $Cys^{10,11,15}$]-hRLX A(1—24) peptide was effected by preparative reverse-phase HPLC on a Waters C—18 Bondapak column using a 0.1% TFA-water/acetonitrile solvent system.

A sample (160 mg) of the peptide purified by gel-filtration was S-sulfonated with a mixture of sodium sulfite and sodium tetrathionate (total reaction time of 3 hours) according to the method described by Du et al., (Scientia Sinica, 10l, 84—104 (1961)). The precipitate which formed during the S-sulfonation reaction was removed by filtration and both the precipitate and the supernatant solution dialyzed against distilled water at 4°C for 48 hours. The contents of the dialysis bags were lyophilized to yield 81.4 mg of peptide from the supernatant solution and 53.2 mg of peptide from the precipitate which occurred during the S-sulfonation reaction. A sample of the 'soluble' [S-sulfo $Cys^{10,11,15,24}$] hRLX A(1—24) peptide was purified by ion exchange chromatography on DEAE-cellulose in tris-HCl buffer pH 8.3. Peptide was eluted from the column with a linear gradient of NaCl in tris-HCl buffer using a conductivity range of 3.0 mS to 85.0 mS. Fractions representing the major peak eluting from the ion-exchange column at conductivity 20 to 30 mS were dialyzed and the peptide recovered by lyophilization. Prepared HPLC was used to further purify the S-sulfonated peptide.

(ii) Synthesis of shortened human relaxin B-chain, hRLX B(1—25)

The amino acid sequence corresponding to residues 1 to 25 of the human relaxin B-chain was synthesized using the procedures described above and commencing with 7.0 gm N-α-tertiarybutyloxy-carbonyl-O-benzyl-L-serine-phenylacetamido-methyl polystyrene resin with a loading of 0.1 mmole Ser per gm. The side-chain protecting groups used in the A-chain synthesis were also employed for the B-chain including the S-ethyl derivative for both cysteines at positions 10 and 22. The aspartic acid residues at positions 4 and 5 were added as the N-α-BOC-ξ-benzyl ester derivative. The glutamine at position 18 was coupled by the active ester procedure using N-α-BOC-L-glutamine-p-nitrophenyl ester in DMF. Following coupling of the tryptophan at position 2, 0.1% indole was added to the trifluoroacetic acid deprotecting reagent and to the subsequent methylene chloride washes.

The final weight of peptide-resin after removal of the BOC group from the amino terminal lysine residue and vacuum-drying was 12.2 gm. A portion of the peptide resin (5 gm) was treated with anhydrous hydrogen fluoride in the presence of anisole (2 ml) at 0°C for 30 minutes and the B-chain peptide isolated using the procedure described above for the A-chain. The crude [S-thioethyl $Cys^{10,22}$] hRLX B(1—25) (1.40 gm) was purified by gel filtration on BioGel P10 in 0.1M acetic acid followed by preparative HPLC.

A sample (150 mg) of the peptide purified by gel filtration was S-sulfonated at pH 8.3 for 3 hours, the reaction mixture filtered and the precipitate and supernatant solutions dialyzed against distilled water. The 'soluble' peptide recovered after lyophilization was 92 mg; the 'insoluble' peptide was 55 mg. The S-sulfonated B-chain peptides were further purified by preparative HPLC using a C—18 reverse-phase column and 0.1% TFA-water-acetonitrile solvent system.

(iii) Chain Combination

The synthetic hRLX A(1—24) and hRLX B(1—25) peptides were combined using the procedure described by Chance and Hoffmann (Australian Patent Application No. 68844/81) for insulin chains wherein the S-sulfonated peptides were mixed in a ratio of A:B of 2:1 at a peptide concentration of 10 mg/ml in glycine buffer pH 10.5. Dithiothreitol in glycine buffer was then added in an amount to give a total of 1.0 sulfhydryl groups for each S-sulfo group. The reaction mixture was then stirred in an open vessel for 24 hours.

As a further modification to this procedure we have found that the chain combination reaction to form biologically active relaxin proceeded efficiently when one or preferably both of the peptide chains are used as their S-thioethyl-Cys derivatives rather than in the S-sulfo form specified by Chance and Hoffmann (op. cit.) in the case of insulin. The use of S-thioethyl Cys peptides eliminates a reaction and purification step required to convert the peptides to the S-sulfo derivatives. In our experience the S-sulfonation reaction of relaxin peptides is accompanied by side reactions which render the S-sulfo relaxins difficult to purify resulting in low yields.

Using the above conditions chain combination yields from 0.24 to 3.1% have been achieved as measured by biological activity in the rat uterine contractility assay of Wiqvist & Paul (Acta Endocrinol., *29*, 135—136, 1958).

Example of Chain Combination Reaction

Human relaxin [S-thioethyl $Cys^{10,11,15}$] A(1—24) (3.60 mg dry wt., 2.0 mg peptide by amino acid analysis, 0.68 µmole) was dissolved in 200 µl of 0.1M glycine buffer pH 10.5 in a 3 ml stoppered plastic centrifuge tube. Human relaxin [S-sulfo $Cys^{10,11}$] B(1—25) (1.89 mg, 1.0 mg peptide by amino acid analysis, 0.33 µmole) dissolved in 100 µl of 0.1M glycine buffer pH 10.5 was added and the mixture agitated. An aliquot (15.2 µl, 1.73 µmole DTT) of a stock solution of dithithreitol (DTT) made up in 0.1 M glycine buffer pH 10.5 (1.15 µmole DTT in 10 ml) was added to the peptide solution and following a brief agitation the reaction mixture was allowed to stand at 4°C for 24 hours open to the air. The mixture was then centrifuged and an aliquot of the supernatant solution tested for relaxin biological activity in the rat uterine contractility assay. Aliquots of the reaction mixture inhibited the spontaneous contractions of the rat uterus in a dose-

related manner. A 75 µl aliquot completely inhibited uterine contractions equivalent to a chain combination yield of 0.70% as compared to a native pig relaxin A22 B31 standard.

Additional synthetic human relaxin peptides based upon the H1-gene sequence:

The synthetic relaxin peptides listed in the following table were prepared from the amino acid sequences for the A and B chains derived from the H1 human relaxin gene sequence shown in Figure 2. The separate peptide chains were prepared and purified according to the procedure described above for the A(1—24) and B(1—25) peptides. A modification of these procedures was used for the B(3—25) amide and B(1—25) amide peptides, wherein the PAM resin linkage was replaced by the benzhydrylamine (BHA) polystyrene resin. Use of the BHA resin results in the formation of peptides with the C-terminus in the amide rather than free carboxy form.

Unless otherwise stated the chain combination reaction was performed as described previously with the A-chain as the S-thioethyl Cys derivative and the B-chain as the S-sulfo Cys derivative.

All of the synthetic analogues in the following table exhibited relaxin-like biological activity in the rat uterine contractility assay. The combination yields of the separate peptide chains were calculated from the bioassay results using native pig relaxin A(1—22)—B(1—31) as standard.

TABLE

Synthetic H1 Human Relaxin Analogue	Combination Yield (based on B-chain amount)
A(1-24) + B(1-23)	0.24%
A(1-24) + B(1-25)	0.70%
A(1-24) + [Ala^{24}]B(1-26)	0.92%
A(1-24) + B(1-32)	2.00%
A(1-24) + B(1-25) amide	0.80%
A(1-24) + B(1-25) amide with both chains in S-thioethyl form for chain combination reaction	3.10%
A(1-24) + B(3-25) amide	0.68%
A(1-24) + [N-formyl Trp^{2}]B(2-25)	0.43%

The features disclosed in the foregoing description, in the following claims and/or in the accompanying drawings may, both separately and in any combination thereof, be material for realising the invention in diverse forms thereof.

References

1. Hisaw, F. L, Proc. Soc. Exp. Biol. Med. *23*, 661—663 (1926).
2. Schwabe, C., McDonald, J. K. and Steinetz, B. C. Biochem. Biophys. Res. Commun. *75*, 503—510 (1977).
3. James, R., Niall, H., Kwok, S. and Bryant-Greenwood, G. Nature, *267*, 544—546 (1977).
4. John, M. J., Walsh, J. R., Borjesson, B. W. and Niall, H. D. Endocrinology *108*, 726—729 (1981).
5. Schwabe, C., Gowan, L. K. and Reinig, J. W., Ann. N.Y. Acad. Sci. *380*, 6—12 (1982).
6. Hudson, P., Haley, J., Cronk, M., Shine, J. and Niall, H. Nature, *291*, 127—131 (1981).
7. Haley, J., Hudson, P., Scanlon, D., John, M., Cronk, M., Shine, J., Tregear, G. and Niall, H. DNA 1, 155—162 (1982).
8. Dayhoff, M. O., Schwartz, R. M., Chen, H. R., Hunt, L. T., Barker, W. C. and Orcutt, B. C. DNA *1*, 51—58 (1981).
9. Lawn, R. M., Fritsch, E. F., Parker, R. C. Blake, G. and Maniatis, T. Cell, *15*, 1157—1174 (1978).
10. Maniatis T., Hardison, R. E., Lacy, E., Lauer, J., O'Connell, C., and Quon, D. Cell *15*, 687—701 (1978).
11. Taylor, J. M., Illmersee, R., and Summers, J. Biochim. Biophys. Acta *442*, 324—330 (1976).
12. Benton, W. D. and Davis, R. Science *196*, 180—183 (1977).
13. Denhardt, D. T. Biochem. Biophys. Res. Commun. *23*, 641—646 (1966).
14. Yamamoto, K. R. and Alberts, B. M. Virology *40*, 734—744 (1970).

References — continued

15. Sanger, F., Coulson, A. R., Barrell, B. G., Smith A. J. A. and Roe, B. A. J. Mol. Biol. *143*, 161—178 (1980).
16. Sanger, F., Nicklen, S. and Coulson, A. R. Proc. Natn. Acad. Sci. *74*, 5463—5467 (1977).
17. Maxam, A. M. and Gilbert, W. Proc. Natn. Acad. Sci. *74*, 560—564 (1977).
18. Staden, R. Nucl. Acids, Res. *6*, 2601—2610 (1979).

Claims

1. A DNA fragment encoding human H1-preprorelaxin, characterized in that it comprises a coding strand and a complementary strand corresponding to the following complete mRNA sequence:

AUG CCU CGC CUG UUC UUG UUC CAC CUG CUA GAA UUC UGU UUA
CUA CUG AAC CAA UUU UCC AGA GCA GUC GCG GCC AAA UGG AAG
GAC GAU GUU AUU AAA UUA UGC GGC CGC GAA UUA GUU CGC GCG
CAG AUU GCC AUU UGC GGC AUG AGC ACC UGG AGC AAA AGG UCU
CUG AGC CAG GAA GAU GCU CCU CAG ACA CCU AGA CCA GUG GCA
GAA AUU GUA CCA UCC UUC AUC AAC AAA GAU ACA GAA ACU AUA
AUU AUC AUG UUG GAA UUC AUU GCU AAU UUG CCA CCG GAG CUG
AAG GCA GCC CUA UCU GAG AGG CAA CCA UCA UUA CCA GAG CUA
CAG CAG UAU GUA CCU GCA UUA AAG GAU UCC AAU CUU AGC UUU
GAA GAA UUU AAG AAA CUU AUU CGC AAU AGG CAA AGU GAA GCC
GCA GAC AGC AAU CCU UCA GAA UUA AAA UAC UUA GGC UUG GAU
ACU CAU UCU CAA AAA AAG AGA CGA CCC UAC GUG GCA CUG UUU
GAG AAA UGU UGC CUA AUU GGU UGU ACC AAA AGG UCU CUU GCU
AAA UAU UGC UGA

2. A DNA fragment encoding human H1-prorelaxin, characterized in that it comprises a coding strand and a complementary strand corresponding to the following complete mRNA sequence:

AAA UGG AAG GAC GAU GUU AUU AAA UUA UGC GGC CGC GAA UUA
GUU CGC GCG CAG AUU GCC AUU UGC GGC AUG AGC ACC UGG AGC
AAA AGG UCU CUG AGC CAG GAA GAU GCU CCU CAG ACA CCU AGA
CCA GUG GCA GAA AUU GUA CCA UCC UUC AUC AAC AAA GAU ACA
GAA ACU AUA AUU AUC AUG UUG GAA UUC AUU GCU AAU UUG CCA
CCG GAG CUG AAG GCA GCC CUA UCU GAG AGG CAA CCA UCA UUA
CCA GAG CUA CAG CAG UAU GUA CCU GCA UUA AAG GAU UCC AAU
CUU AGC UUU GAA GAA UUU AAG AAA CUU AUU CGC AAU AGG CAA
AGU GAA GCC GCA GAC AGC AAU CCU UCA GAA UUA AAA UAC UUA
GGC UUG GAU ACU CAU UCU CAA AAA AAG AGA CGA CCC UAC GUG
GCA CUG UUU GAG AAA UGU UGC CUA AUU GGU UGU ACC AAA AGG
UCU CUU GCU AAA UAU UGC UGA

3. A DNA fragment as claimed in Claim 2, which is a double-stranded DNA fragment encoding the signal, A, B or C peptide chains of human H1-preprorelaxin or a combination of any to or more of said chains characterized in that it comprises a coding strand and a complementary strand corresponding to the appropriate mRNA sequence or combination of the mRNA sequences given below:

Signal Peptide

AUG CCU CGC CUG UUC UUG UUC CAC CUG CUA GAA UUC UGU UUA
CUA CUG AAC CAA UUU UCC AGA GCA GUC GCG GCC

A-Chain

CGA CCC UAC GUG GCA CUG UUU GAG AAA UGU UGC CUA AUU GGU
UGU ACC AAA AGG UCU CUU GCU AAA UAU UGC

B-Chain

AAA UGG AAG GAC GAU GUU AUU AAA UUA UGC GGC CGC GAA UUA
GUU CGC GCG CAG AUU GCC AUU UGC GGC AUG AGC ACC UGG AGC
AAA AGG UCU CUG

C-Chain

AGC CAG GAA GAU GCU CCU CAG ACA CCU AGA CCA GUG GCA GAA
AUU GUA CCA UCC UUC AUC AAC AAA GAU ACA GAA ACU AUA AUU
AUC AUG UUG GAA UUC AUU GCU AAU UUG CCA CCG GAG CUG AAG
GCA GCC CUA UCU GAG AGG CAA CCA UCA UUA CCA GAG CUA CAG
CAG UAU GUA CCU GCA UUA AAG GAU UCC AAU CUU AGC UUU GAA
GAA UUU AAG AAA CUU AUU CGC AAU AGG CAA AGU GAA GCC GCA
GAC AGC AAU CCU UCA GAA UUA AAA UAC UUA GGC UUG GAU ACU
CAU UCU CAA AAA AAG AGA

4. A process for the production of a DNA fragment as set out in any one of Claims 1 to 3, characterized in that it comprises screening a human genomic clone bank using as a probe a fragment of porcine relaxin cDNA having the following nucleotide sequence which corresponds to amino acids 45—95 in the C-peptide thereof:

GCA GAA ACC ATG CCA TCC TCC ATC ACC AAA GAT GCA GAA ATC
TTA AAG ATG ATG TTG GAA TTT GTT CCT AAT TTG CCA CAG GAG
CTG AAG GCA ACA TTG TCT GAG AGG CAA CCA TCA CTG AGA GAG
CTA CAA CAA TCT GCA TCA AAG GAT TCG.

5. A DNA transfer vector, characterized in that it contains a cDNA deoxynucleotide sequences corresponding to a DNA fragment as defined in any one of Claims 1 to 3.

6. A DNA fragment or DNA transfer vector as claimed in any of Claims 1 to 3 and 5, characterized in that one or more natural codons or their cDNA equivalents of said DNA fragments are replaced by another codon which codes for the same amino acid.

7. A DNA transfer vector as claimed in any one of Claims 5 or 6, characterized in that it is a bacterial plasmid.

8. A DNA transfer vector as claimed in any one of Claims 5 to 7 which is bacteriophage DNA.

9. A cell transformed by a transfer vector as claimed in any one of Claims 5 to 8.

10. A process for making a DNA transfer vector for use in maintaining and replicating a DNA fragment as claimed in any one of claims 1 to 3 and 6, characterized in that it comprises reacting the appropriate deoxynucleotide sequence of the said DNA fragment with a DNA molecule prepared by cleaving a transfer vector with a restriction enzyme.

11. A process for making a fusion protein comprising an amino acid sequence consisting of all or part of the amino acid sequence of human H1-preprorelaxin as its C-terminal sequence and a portion of a prokaryotic protein as its N-terminal sequence, characterized in that it comprises incubating a microorganism transformed by an expression transfer vector comprising the appropriate deoxynucleotide sequence.

12. A process for synthesizing human H1-prorelaxin comprising the A and B peptides separated from each other by a C peptide, characterized inthat it comprises incubating a microorganism, transformed by an

expression transfer vector comprising a DNA fragment coding for said human prorelaxin as claimed in Claim 2 under conditions suitable for expression of said DNA fragment, and purifying human prorelaxin from the lysate or culture medium of said microorganism.

13. A polypeptide with human H1-preprorelaxin activity, said polypeptide being selected from the following group:

(a) a polypeptide having the amino acid sequence shown in Figure 2 A and B that corresponds to human H1-preprorelaxin;

(b) a polypeptide that in respect to (a) is deficient in one or more amino acids;

(c) a polypeptide in which in respect to (a) one or more amino acids are replaced with different amino acids;

(d) a polypeptide in which in respect to (a) one or more amino acids are added to the sequence; or

(e) a fusion polypeptide comprising an amino acid sequence consisting of all or part of the amino acid sequence of human H1-preprorelaxin shown in Figure 2 A and B as its C-terminal sequence and a portion of a prokaryotic protein as its N-terminal sequence.

14. A polypeptide with human H1-prorelaxin activity, said polypeptide being selected from the following group:

(a) a polypeptide having the amino acid sequence shown in Figure 2 A and B that corresponds to human H1-prorelaxin;

(b) a polypeptide that in respect to (a) is deficient in one or more amino acids;

(c) a polypeptide in which in respect to (a) one or more amino acids are replaced with different amino acids;

(d) a polypeptide in which in respect to (a) one or more amino acids are added to the sequence; or

(e) a fusion polypeptide comprising an amino acid sequence consisting of all or part of the amino acid sequence of human H1-prorelaxin shown in Figure 2 A and B as its C-terminal sequence and a portion of a prokaryotic protein as its N-terminal sequence.

15. A polypeptide with human H1-relaxin activity, said polypeptide being selected from the following group:

(a) a polypeptide having the amino acid sequence shown in Figure 2 A and B that corresponds to human H1-relaxin except that it is deficient in one or more amino acids;

(b) a polypeptide having the amino acid sequence shown in Figure 2 A and B that corresponds to human H1-relaxin except that one or more amino acids are replaced with different amino acids;

(c) a polypeptide having the amino acid sequence shown in Figure 2 A and B that corresponds to human H1-relaxin except that one or more amino acids are added to the sequence; or

(d) a fusion polypeptide comprising an amino acid sequence consisting of all or part of the amino acid sequence of human H1-relaxin shown in Figure 2 A and B as its C-terminal sequence and a portion of a prokaryotic protein as its N-terminal sequence.

16. A process for the isolation of a chromosomal relaxin gene encoding a human H1-relaxin according to claim 15, characterized in that it comprises screening a genomic library using as a probe a sub-unit of the porcine relaxin cDNA.

17. An isolated DNA sequence comprising a DNA sequence encoding human H1-preprorelaxin, human H1-prorelaxin, or human H1-relaxin which has been modified by deletion of one or more of the natural codons, to encode a peptide comprising an A chain selected from the group consisting of A chain amino acids 1—24 to 3—24 and a B chain selected from the group consisting of B chain amino acids 1—32 to 4—23, said peptide having human H1-relaxin activity.

18. An isolated DNA sequence comprising a DNA sequence encoding human H1-preprorelaxin, human H1-prorelaxin or human H1-relaxin which has been modified by replacement of one or more of the natural codons by codons which code for amino acids other than that coded by the natural codon, to encode a peptide comprising an A chain selected from the group consisting of A chain amino acids 1—24 to 3—24 and a B chain selected from the group consisting of B chain amino acids 1—32 to 4—23, wherein the Met 24 of the B chain is substituted with Ala, Val, Gly or Ser, said peptide having human H1-relaxin activity.

19. A DNA fragment encoding a polypeptide with human H1-preprorelaxin activity, said polypeptide being selected from the following group:

(a) a polypeptide having the amino acid sequence shown in Figure 2 A and B that corresponds to human H1-preprorelaxin;

(b) a polypeptide that in respect to (a) is deficient in one or more amino acids;

(c) a polypeptide in which in respect to (a) one or more amino acids are replaced with different amino acids;

(d) a polypeptide in which in respect to (a) one or more amino acids are added to the sequence; or

(e) a fusion polypeptide comprising an amino acid sequence consisting of all or part of the amino acid sequence of human H1-preprorelaxin shown in Figure 2 A and B as its C-terminal sequence and a portion of a prokaryotic protein as its N-terminal sequence.

20. A DNA fragment encoding a polypeptide with human H1-prorelaxin activity, said polypeptide being selected from the following group:

(a) a polypeptide having the amino acid sequence shown in Figure 2 A and B that corresponds to human H1-prorelaxin;

(b) a polypeptide that in respect to (a) is deficient in one or more amino acids;
(c) a polypeptide in which in respect to (a) one or more amino acids are replaced with different amino acids;
(d) a polypeptide in which in respect to (a) one or more amino acids are added to the sequence; or
(e) a fusion polypeptide comprising an amino acid sequence consisting of all or part of the amino acid sequence of human H1-prorelaxin shown in Figure 2 A and B as its C-terminal sequence and a portion of a prokaryotic protein as its N-terminal sequence.

21. An isolated DNA fragment encoding a polypeptide with human H1-relaxin activity, said polypeptide being selected from the following group:
(a) a polypeptide having the amino acid sequence shown in Figure 2 A and B that corresponds to human H1-relaxin;
(b) a polypeptide that in respect to (a) is deficient in one or more amino acids;
(c) a polypeptide in which in respect to (a) one or more amino acids are replaced with different amino acids;
(d) a polypeptide in which in respect to (a) one or more amino acids are added to the sequence; or
(e) a fusion polypeptide comprising an amino acid sequence consisting of all or part of the amino acid sequence of human H1-relaxin shown in Figure 2 A and B as its C-terminal sequence and a portion of a prokaryotic protein as its N-terminal sequence.

Patentansprüche

1. DNA-Fragment, das menschliches H1-Präprorelaxin codiert dadurch gekennzeichnet, daß es einen codierenden Strang und einen komplementären Strang, entsprechend der folgenden vollständigen mRNA-Sequenz, umfaßt:

AUG CCU CGC CUG UUC UUG UUC CAC CUG CUA GAA UUC UGU UUA
CUA CUG AAC CAA UUU UCC AGA GCA GUC GCG GCC AAA UGG AAG
GAC GAU GUU AUU AAA UUA UGC GGC CGC GAA UUA GUU CGC GCG
CAG AUU GCC AUU UGC GGC AUG AGC ACC UGG AGC AAA AGG UCU
CUG AGC CAG GAA GAU GCU CCU CAG ACA CCU AGA CCA GUG GCA
GAA AUU GUA CCA UCC UUC AUC AAC AAA GAU ACA GAA ACU AUA
AUU AUC AUG UUG GAA UUC AUU GCU AAU UUG CCA CCG GAG CUG
AAG GCA GCC CUA UCU GAG AGG CAA CCA UCA UUA CCA GAG CUA
CAG CAG UAU GUA CCU GCA UUA AAG GAU UCC AAU CUU AGC UUU
GAA GAA UUU AAG AAA CUU AUU CGC AAU AGG CAA AGU GAA GCC
GCA GAC AGC AAU CCU UCA GAA UUA AAA UAC UUA GGC UUG GAU
ACU CAU UCU CAA AAA AAG AGA CGA CCC UAC GUG GCA CUG UUU
GAG AAA UGU UGC CUA AUU GGU UGU ACC AAA AGG UCU CUU GCU
AAA UAU UGC UGA

2. DNA-Fragment, das menschliches H1-Prorelaxin codiert, dadurch gekennzeichnet, daß es einen codierenden Strang und einen komplementären Strang, entsprechend der folgenden mRNA-Sequenz, umfaßt:

AAA UGG AAG GAC GAU GUU AUU AAA UUA UGC GGC CGC GAA UUA
GUU CGC GCG CAG AUU GCC AUU UGC GGC AUG AGC ACC UGG AGC
AAA AGG UCU CUG AGC CAG GAA GAU GCU CCU CAG ACA CCU AGA
CCA GUG GCA GAA AUU GUA CCA UCC UUC AUC AAC AAA GAU ACA
GAA ACU AUA AUU AUC AUG UUG GAA UUC AUU GCU AAU UUG CCA
CCG GAG CUG AAG GCA GCC CUA UCU GAG AGG CAA CCA UCA UUA
CCA GAG CUA CAG CAG UAU GUA CCU GCA UUA AAG GAU UCC AAU
CUU AGC UUU GAA GAA UUU AAG AAA CUU AUU CGC AAU AGG CAA
AGU GAA GCC GCA GAC AGC AAU CCU UCA GAA UUA AAA UAC UUA

GGC UUG GAU ACU CAU UCU CAA AAA AAG AGA CGA CCC UAC GUG
GCA CUG UUU GAG AAA UGU UGC CUA AUU GGU UGU ACC AAA AGG
UCU CUU GCU AAA UAU UGC UGA

3. DNA-Fragment nach Anspruch 2, das ein doppelsträngiges DNA-Fragment ist, welches die Signal-, A-, B- oder C-Peptidketten von menschlichem H1-Präprorelaxin oder eine Kombination von jeweils zwei oder mehr besagter Ketten codiert, dadurch gekennzeichnet, daß es einen codierenden Strang und einen komplementären Strang, entsprechend der passenden mRNA-Sequenz oder der Kombination der mRNA-Sequenzen, die unten angegeben sind, umfaßt:

Signalpeptid

AUG CCU CGC CUG UUC UUG UUC CAC CUG CUA GAA UUC UGU UUA
CUA CUG AAC CAA UUU UCC AGA GCA GUC GCG GCC

A-Kette

CGA CCC UAC GUG GCA CUG UUU GAG AAA UGU UGC CUA AUU GGU
UGU ACC AAA AGG UCU CUU GCU AAA UAU UGC

B-Kette

AAA UGG AAG GAC GAU GUU AUU AAA UUA UGC GGC CGC GAA UUA
GUU CGC GCG CAG AUU GCC AUU UGC GGC AUG AGC ACC UGG AGC
AAA AGG UCU CUG

C-Kette

AGC CAG GAA GAU GCU CCU CAG ACA CCU AGA CCA GUG GCA GAA
AUU GUA CCA UCC UUC AUC AAC AAA GAU ACA GAA ACU AUA AUU
AUC AUG UUG GAA UUC AUU GCU AAU UUG CCA CCG GAG CUG AAG
GCA GCC CUA UCU GAG AGG CAA CCA UCA UUA CCA GAG CUA CAG
CAG UAU GUA CCU GCA UUA AAG GAU UCC AAU CUU AGC UUU GAA
GAA UUU AAG AAA CUU AUU CGC AAU AGG CAA AGU GAA GCC GCA
GAC AGC AAU CCU UCA GAA UUA AAA UAC UUA GGC UUG GAU ACU
CAU UCU CAA AAA AAG AGA

4. Verfahren zur Herstellung eines DNA-Fragments nach einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß es das Screenen einer menschlichen Genom-Klonbank unter Verwendung eines Fragments von Schweine-Relaxin-cDNA mit der folgenden Nukleotidsequenz, die den Aminosäuren 45—95 im C-Peptid desselben entspricht, als Sonde umfaßt:

GCA GAA ACC ATG CCA TCC TCC ATC ACC AAA GAT GCA GAA ATC
TTA AAG ATG ATG TTG GAA TTT GTT CCT AAT TTG CCA CAG GAG
CTG AAG GCA ACA TTG TCT GAG AGG CAA CCA TCA CTG AGA GAG
CTA CAA CAA TCT GCA TCA AAG GAT TCG.

5. DNA-Transfervektor, dadurch gekennzeichnet, daß er eine cDNA-Desoxynukleotidsequenz enthält, entsprechend einem DNA-Fragment, wie in einem der Ansprüche 1 bis 3 definiert.

6. DNA-Fragment oder DNA-Transfervektor nach einem der Ansprüche 1 bis 3 und 5, dadurch gekennzeichnet, daß ein oder mehrere natürliche Codons oder deren cDNA-Äquivalente besagter DNA-Fragment durch ein anderes Codon ersetzt sind, welches dieselbe Aminosäure codiert.

7. DNA-Transfervektor nach einem der Ansprüche 5 oder 6, dadurch gekennzeichnet, daß er ein bakterielles Plasmid ist.

8. DNA-Transfervektor nach einem der Ansprüche 5 bis 7, der Bakteriophagen-DNA ist.

9. Zelle, transformiert mit einem Transfervektor nach einem der Ansprüche 5 bis 8.

10. Verfahren zur Herstellung eines DNA-Transfervektors zur Verwendung bei der Aufrechterhaltung und Replikation eines DNA-Fragments nach einem der Ansprüche 1 bis 3 und 6, dadurch gekennzeichnet,

daß es das Umsetzen der passenden Desoxynukleotidsequenz des besagten DNA-Fragments mit einem DNA-Molekül umfaßt, das durch Schneiden eines Transfervektors mit einem Restriktionsenzym hergestellt worden ist.

11. Verfahren zur Herstellung eines Fusionsproteins, das eine Aminosäuresequenz umfaßt, die insgesamt oder teilweise aus einer Aminosäuresequenz von menschlichem H1-Präprorelaxin als seiner C-terminalen Sequenz und eines Teils eines prokaryontischen Proteins als seiner N-terminalen Sequenz besteht, dadurch gekennzeichnet, daß es das Inkubieren eines Mikroorganismus umfaßt, der mit einem Expressions-Transfervektor transformiert ist, welcher die passende Desoxynukleotidsequenz umfaßt.

12. Verfahren zu Synthese von menschlichem H1-Prorelaxin, welches die A- und B-Peptide, getrennt voneinander durch ein C-Peptid, umfaßt, dadurch gekennzeichnet, daß es das Inkubieren eines Mikroorganismus, transformiert mit einem Expressions-Transfervektor, der ein DNA-Fragment umfaßt, das für besagtes menschliches Prorelaxin nach Anspruch 2 kodiert, unter für die Expression besagten DNA-Fragments geeigneten Bedingungen, und das Reinigen menschlichen Prorelaxins aus dem Lysat oder Kulturmedium von besagtem Mikroorganismus umfaßt.

13. Polypeptid mit der Aktivität von menschlichem H1-Präprorelaxin, wobei besagtes Polypeptid ausgewählt ist aus der folgenden Gruppe:

(a) ein Polypeptid mit der in Figur 2 A und B dargestellten Aminosäuresequenz, die menschlichem H1-Präprorelaxin entspricht;

(b) ein Polypeptid, dem im Hinblick auf (a) eine oder mehrere Aminosäuren fehlen;

(c) ein Polypeptid, in dem in Hinblick auf (a) eine oder mehrere Aminosäuren durch andere Aminosäuren ersetzt sind;

(d) ein Polypeptid, in dem im Hinblick auf (a) eine oder mehrere Aminosäuren zur Sequenz hinzugefügt sind; oder

(e) ein Fusions-Polypeptid, das eine Aminosäuresequenz umfaßt, die insgesamt oder teilweise aus der in Figur 2 A und B dargestellten Aminosäuresequenz von menschlichem H1-Präprorelaxin als seiner C-terminalen Sequenz und einem Teil eines prokaryontischen Proteins als seiner N-terminalen Sequenz besteht.

14. Polypeptid mit der Aktivität von menschlichem H1-Prorelaxin, wobei besagtes Polypeptid ausgewählt ist aus der folgenden Gruppe:

(a) ein Polypeptid mit der in Figur 2 A und B dargestellten Aminosäuresequenz, die menschlichem H1-Prorelaxin entspricht;

(b) ein Polypeptid, dem im Hinblick auf (a) eine oder mehrere Aminosäuren fehlen;

(c) ein Polypeptid, in dem in Hinblick auf (a) eine oder mehrere Aminosäuren durch andere Aminosäuren ersetzt sind;

(d) ein Polypeptid, in dem im Hinblick auf (a) eine oder mehrere Aminosäuren zur Sequenz hinzugefügt sind; oder

(e) ein Fusions-Polypeptid, das eine Aminosäuresequenz umfaßt, die insgesamt oder teilweise aus der in Figur 2 A und B dargestellten Aminosäuresequenz von menschlichem H1-Prorelaxin als seiner C-terminalen Sequenz und einem Teil eines prokaryontischen Proteins als seiner N-terminalen Sequenz besteht.

15. Polypeptid mit der Aktivität von menschlichem H1-Relaxin, wobei besagtes Polypeptid ausgewählt ist aus der folgenden Gruppe:

(a) ein Polypeptid mit der in Figur 2 A und B dargestellten Aminosäuresequenz, die menschlichem H1-Relaxin entspricht, mit der Ausnahme, daß ihm eine oder mehrere Aminosäuren fehlen;

(b) ein Polypeptid mit der in Figur 2 A und B dargestellten Aminosäuresequenz, die menschlichem H1-Relaxin entspricht, mit der Ausnahme, daß eine oder mehrere Aminosäuren durch andere Aminosäuren ersetzt sind;

(c) ein Polypeptid mit der in Figur 2 A und B dargestellten Aminosäuresequenz, die menschlichen H1-Relaxin entspricht, mit der Ausnahme, daß eine oder mehrere Aminosäuren zur Sequenz hinzugefügt sind; oder

(d) ein Fusions-Polypeptid, daß eine Aminosäuresequenz umfaßt, die insgesamt oder teilweise aus der in Figur 2 A und B dargestellten Aminosäuresequenz von menschlichem H1-Relaxin als seiner C-terminalen Sequenz und einem Teil eines prokaryontischen Proteins als seiner N-terminalen Sequenz besteht.

16. Verfahren zur Isolierung eines chromosomalen Relaxin-Gens das ein menschliches H1-Relaxin nach Anspruch 15 codiert, dadurch gekennzeichnet, daß es das Screenen einer Genombibliothek unter Verwendung einer Untereinheit der Schweine-Relaxin-cDNA als Sonde umfaßt.

17. Isolierte DNA-Sequenz, die eine DNA-Sequenz umfaßt, welche menschliches H1-Präprorelaxin, menschliches H1-Prorelaxin oder menschliches H1-Relaxin codiert, das durch Deletion einer oder mehrerer natürlicher Codons modifiziert worden ist, um ein Peptid zu codieren, das eine A-Kette, die ausgewählt ist aus der Gruppe, die aus der A-Ketten-Aminosäuren 1—24 bis 3—24 besteht, und eine B-Kette, die ausgewählt ist aus der Gruppe, die aus B-Ketten-Aminosäuren 1—32 bis 4—23 besteht, umfaßt, wobei besagtes Peptid die Aktivität von menschlichem H1-Relaxin besitzt.

18. Isolierte DNA-Sequenz, die eine DNA-Sequenz umfaßt, die menschliches H1-Präprorelaxin, menschliches H1-Prorelaxin oder menschliches H1-Relaxin codiert, das durch Ersetzen einer oder mehrerer natürlicher Codons durch Codons, die für andere Aminosäuren codieren als für diejenigen, die durch das

natürliche Codons codiert werden, modifiziert worden sind, um ein Peptid zu codieren, das eine A-Kette, die ausgewählt ist aus der Gruppe, die aus A-Ketten-Aminosäuren 1—24 bis 3—24 besteht, und eine B-Kette, die ausgewählt ist aus der Gruppe, die aus B-Ketten-Aminosäuren 1—32 bis 4—23 besteht, umfaßt, wobei das Met 24 de B-Kette durch Ala, Val, Gly oder Ser ersetzt ist, wobei besagtes Peptid die Aktivität von menschlichem H1-Relaxin besitzt.

19. DNA-Fragment, das ein Polypeptid mit der Aktivität von menschlichem H1-Präprorelaxin codiert, wobei besagtes Polypeptid ausgewählt ist aus der folgenden Gruppe:

(a) ein Polypeptid mit der in Figur 2 A und B dargestellten Aminosäuresequenz, die menschlichem H1-Präprorelaxin entspricht;

(b) ein Polypeptid, dem im Hinblick auf (a) eine oder mehrere Aminosäuren fehlen;

(c) ein Polypeptid, in dem im Hinblick auf (a) eine oder mehrere Aminosäuren durch andere Aminosäuren ersetzt sind;

(d) ein Polypeptid, in dem im Hinblick auf (a) eine oder mehrere Aminosäuren zur Sequenz hinzugefügt sind; oder

(e) ein Fusions-Polypeptid, das eine Aminosäuresequenz umfaßt, die insgesamt oder teilweise aus der in Figur 2 A und B dargestellten Aminosäuresequenz von menschlichem H1-Präprorelaxin als seiner C-terminalen Sequenz und einem Teil eines prokaryontischen Proteins als seiner N-terminalen Sequenz besteht.

20. DNA-Fragment, das ein Polypeptid mit der Aktivität von menschlichem H1-Prorelaxin codiert, wobei besagtes Polypeptid ausgewählt ist aus der folgenden Gruppe:

(a) ein Polypeptid mit der in Figur 2 A und B dargestellten Aminosäuresequenz, die menschlichem H1-Prorelaxin entspricht;

(b) ein Polypeptid, dem im Hinblick auf (a) eine oder mehrere Aminosäuren fehlen;

(c) ein Polypeptid, in dem im Hinblick auf (a) eine oder mehrere Aminosäuren durch andere Aminosäuren ersetzt sind;

(d) ein Polypeptid, in dem im Hinblick auf (a) eine oder mehrere Aminosäuren zur Sequenz hinzugefügt sind; oder

(e) ein Fusions-Polypeptid, das eine Aminosäuresequenz umfaßt, die insgesamt oder teilweise aus der in Figur 2 A und B dargestellten Aminosäuresequenz von menschlichem H1-Prorelaxin als seiner C-terminalen Sequenz und einem Teil eines prokaryontischen Proteins als seiner N-terminalen Sequenz besteht.

21. Isoliertes DNA-Fragment, das ein Polypeptid mit der Aktivität von menschlichem H1-Relaxin codiert, wobei besagtes Polypeptid ausgewählt ist aus der folgenden Gruppe:

(a) ein Polypeptid mit der in Figur 2 A und B dargestellten Aminosäuresequenz, die menschlichem H1-Relaxin entspricht,

(b) ein Polypeptid, dem im Hinblick auf (a) eine oder mehrere Aminosäuren fehlen;

(c) ein Polypeptid, dem im Hinblick auf (a) eine oder mehrere Aminosäuren durch andere Aminosäuren ersetzt sind;

(d) ein Polypeptid, in dem im Hinblick auf (a) eine oder mehrere Aminosäuren zur Sequenz hinzugefügt sind; oder

(e) ein Fusions-Polypeptid, das eine Aminosäuresequenz umfaßt, die insgesamt oder teilweise aus der in Figur 2 A und B dargestellten Aminosäuresequenz von menschlichem H1-Relaxin als seiner C-terminalen Sequenz und einem Teil eines prokaryontischen Proteins als seiner N-terminalen Sequenz besteht.

Revendications

1. Fragment d'ADN codant pour la préprorelaxine-H1 humaine, caractérisé en ce qu'il comprend un brin codant et un brin complémentaire correspondant à la séquence complète d'ARNm suivante:

AUG CCU CGC CUG UUC UUG UUC CAC CUG CUA GAA UUC UGU UUA
CUA CUG AAC CAA UUU UCC AGA GCA GUC GCG GCC AAA UGG AAG
GAC GAU GUU AUU AAA UUA UGC GGC CGC GAA UUA GUU CGC GCG
CAG AUU GCC AUU UGC GGC AUG AGC ACC UGG AGC AAA AGG UCU
CUG AGC CAG GAA GAU GCU CCU CAG ACA CCU AGA CCA GUG GCA
GAA AUU GUA CCA UCC UUC AUC AAC AAA GAU ACA GAA ACU AUA
AUU AUC AUG UUG GAA UUC AUU GCU AAU UUG CCA CCG GAG CUG
AAG GCA GCC CUA UCU GAG AGG CAA CCA UCA UUA CCA GAG CUA
CAG CAG UAU GUA CCU GCA UUA AAG GAU UCC AAU CUU AGC UUU
GAA GAA UUU AAG AAA CUU AUU CGC AAU AGG CAA AGU GAA GCC

GCA GAC AGC AAU CCU UCA GAA UUA AAA UAC UUA GGC UUG GAU
ACU CAU UCU CAA AAA AAG AGA CGA CCC UAC GUG GCA CUG UUU
GAG AAA UGU UGC CUA AUU GGU UGU ACC AAA AGG UCU CUU GCU
AAA UAU UGC UGA

2. Fragment d'ADN codant pour la prorelaxine-H1 humaine, caractérisé en ce qu'il comprend un brin codant et un brin complémentaire correspondant à la séquence d'ARNm suivante:

AAA UGG AAG GAC GAU GUU AUU AAA UUA UGC GGC CGC GAA UUA
GUU CGC GCG CAG AUU GCC AUU UGC GGC AUG AGC ACC UGG AGC
AAA AGG UCU CUG AGC CAG GAA GAU GCU CCU CAG ACA CCU AGA
CCA GUG GCA GAA AUU GUA CCA UCC UUC AUC AAC AAA GAU ACA
GAA ACU AUA AUU AUC AUG UUG GAA UUC AUU GCU AAU UUG CCA
CCG GAG CUG AAG GCA GCC CUA UCU GAG AGG CAA CCA UCA UUA
CCA GAG CUA CAG CAG UAU GUA CCU GCA UUA AAG GAU UCC AAU
CUU AGC UUU GAA GAA UUU AAG AAA CUU AUU CGC AAU AGG CAA
AGU GAA GCC GCA GAC AGC AAU CCU UCA GAA UUA AAA UAC UUA
GGC UUG GAU ACU CAU UCU CAA AAA AAG AGA CGA CCC UAC GUG
GCA CUG UUU GAG AAA UGU UGC CUA AUU GGU UGU ACC AAA AGG
UCU CUU GCU AAA UAU UGC UGA

3. Fragment d'ADN selon la revendication 2, consistant en un fragment d'ADN bicaténaire codant pour les chaînes peptidiques signal, A, B ou C de la préprorelaxine-H1 humaine, ou pour une combinaison d'au moins deux de ces chaînes, caractérisé en ce qu'il comprend un brin codant et un brin complémentaire correspondant à la séquence d'ARNm appropriée, ou à une combinaison des séquences d'ARNm mentionnées ci-dessous:

Peptide signal

AUG CCU CGC CUG UUC UUG UUC CAC CUG CUA GAA UUC UGU UUA
CUA CUG AAC CAA UUU UCC AGA GCA GUC GCG GCC

Chaîne A

CGA CCC UAC GUG GCA CUG UUU GAG AAA UGU UGC CUA AUU GGU
UGU ACC AAA AGG UCU CUU GCU AAA UAU UGC

Chaîne B

AAA UGG AAG GAC GAU GUU AUU AAA UUA UGC GGC CGC GAA UUA
GUU CGC GCG CAG AUU GCC AUU UGC GGC AUG AGC ACC UGG AGC
AAA AGG UCU CUG

Chaîne C

AGC CAG GAA GAU GCU CCU CAG ACA CCU AGA CCA GUG GCA GAA
AUU GUA CCA UCC UUC AUC AAC AAA GAU ACA GAA ACU AUA AUU
AUC AUG UUG GAA UUC AUU GCU AAU UUG CCA CCG GAG CUG AAG
GCA GCC CUA UCU GAG AGG CAA CCA UCA UUA CCA GAG CUA CAG
CAG UAU GUA CCU GCA UUA AAG GAU UCC AAU CUU AGC UUU GAA
GAA UUU AAG AAA CUU AUU CGC AAU AGG CAA AGU GAA GCC GCA

GAC AGC AAU CCU UCA GAA UUA AAA UAC UUA GGC UUG GAU ACU

CAU UCU CAA AAA AAG AGA

4. Procédé de production d'un fragment d'ADN selon l'une quelconque des revendications 1 à 3, caractérisé en ce qu'on crible une banque de clones de gènes en employant comme sonde, un fragment d'ADNc de relaxine porcine ayant la séquence nucléotidique suivante qui correspond aux aminoacides 45 à 95 du peptide C correspondant:

GCA GAA ACC ATG CCA TCC TCC ATC ACC AAA GAT GCA GAA

ATC TTA AAG ATG ATG TTG GAA TTT GTT CCT AAT TTG CCA

CAG GAG CTG AAG GCA ACA TTG TCT GAG AGG CAA CCA TCA

CTG AGA GAG CTA CAA CAA TCT GCA TCA AAG GAT TCG

5. Vecteur de transfert d'ADN, caractérisé en ce qu'il contient des séquences de désoxynucléotides d'ADNc, correspondant à un fragment selon l'une quelconque des revendications 1 à 3.

6. Fragment d'ADN ou vecteur de transfert d'ADN selon l'une quelconque des revendications 1 à 3 et 5, caractérisé en ce qu'un ou plusieurs codons naturels ou leurs ADNc équivalents de ces fragments d'ADN, sont remplacés par un autre codon qui code pour le même aminoacide.

7. Vecteur de transfert d'ADN selon l'une quelconque des revendications 5 et 6, caractérisé en ce qu'il est un plasmide bactérien.

8. Vecteur de transfert d'ADN selon l'une quelconque des revendications 5 à 7, consistant en un ADN de bactériophage.

9. Cellule transformée par un vecteur de transfert selon l'une quelconque des revendications 5 à 8.

10. Procédé de préparation d'un vecteur de transfert d'ADN destiné à être employé pour maintenir et répliquer un fragment d'ADN selon l'une quelconque des revendications 1 à 3 et 6, caractérisé en ce qu'on fait réagir la séquence de désoxynucléotides appropriée dudit fragment d'ADN, avec une molécule d'ADN préparée par clivage d'un vecteur de transfert avec une enzyme de restriction.

11. Procédé de préparation d'une protéine fusionnée, comprenant une séquence d'aminoacides consistant en totalité ou en partie en la séquence d'aminoacides de la préprorelaxine-H1 humaine formant sa séquence C-terminale, et une partie d'une protéine procaryote formant sa séquence N-terminale, caractérisé en ce qu'on incube un micro-organisme transformé par un vecteur de transfert d'expression comprenant la séquence de désoxynucléotides appropriée.

12. Procédé de synthèse de la prorelaxine-H1 humaine comprenant les peptides A et B séparés l'un de l'autre par un peptide C, caractérisé en ce qu'on incube un micro-organisme transformé par un vecteur de transfert et d'expression comprenant un fragment d'ADN codant pour la prorelaxine humaine défini dans la revendication 2, dans des conditions appropriées pour permettre l'expression dudit fragment d'ADN, et on purifie la prorelaxine humaine à partir du lysat ou du milieu de culture de ce micro-organisme.

13. Polypeptide ayant l'activité de la préprorelaxine-H1 humaine, ce polypeptide étant choisi parmi le groupe suivant:

(a) un polypeptide ayant la séquence d'aminoacides illustrée sur les figures 2A et 2B, correspondant à la préprorelaxine-H1 humaine;

(b) un polypeptide correspondant au polypeptide (a) avec un ou plusieurs aminoacides en moins;

(c) un polypeptide correspondant au polypeptide (a) dans lequel un ou plusieurs aminoacides sont remplacés par des aminoacides différents;

(d) un polypeptide correspondant au polypeptide (a) à la séquence duquel un ou plusieurs aminoacides sont ajoutés; ou

(e) un polypeptide fusionné comprenant une séquence d'aminoacides consistant en totalité ou en partie en la séquence d'aminoacides de la préprorelaxine-H1 humaine illustrée sur les figures 2A et 2B formant sa séquence C-terminale, et une partie d'une protéine procaryote formant sa séquence N-terminale.

14. Polypeptide ayant l'activité de la prorelaxine-H1 humaine, ce polypeptide étant choisi parmi le groupe suivant:

(a) un polypeptide ayant la séquence d'aminoacides illustrée sur les figures 2A et 2B, correspondant à la prorelaxine-H1 humaine;

(b) un polypeptide correspondant au polypeptide (a) avec un ou plusieurs aminoacides en moins;

(c) un polypeptide correspondant au polypeptide (a) dans lequel un ou plusieurs aminoacides sont remplacés par des aminoacides différents;

(d) un polypeptide correspondant au polypeptide (a) à la séquence duquel un ou plusieurs aminoacides sont ajoutés; ou

(e) un polypeptide fusionné comprenant une séquence d'aminoacides consistant en totalité ou en partie, en la séquence d'aminoacides de la prorelaxine-H1 humaine illustrée sur les figures 2A et 2B, formant sa séquence C-terminale, et une partie d'une protéine procaryote formant sa séquence N-terminale.

15. Polypeptide ayant l'activité de la relaxine-H1 humaine, ce polypeptide étant choisi parmi le groupe suivant:

(a) un polypeptide ayant la séquence d'aminoacides illustrée sur les figures 2A et 2B, correspondant à la relaxine-H1 humaine avec un ou plusieurs aminoacides en moins;

(b) un polypeptide ayant la séquence d'aminoacides illustrée sur les figures 2A et 2B correspondant à la relaxine-H1 humaine dans laquelle un ou plusieurs aminoacides sont remplacés par des aminoacides différents;

(c) un polypeptide ayant la séquence d'aminoacides illustrée sur les figures 2A et 2B, correspondant à la relaxine-H1 humaine à la séquence de laquelle un ou plusieurs aminoacides sont ajoutés; ou

(d) un polypeptide fusionné comprenant une séquence d'aminoacides consistant en totalité ou en partie, en la séquence d'aminoacides de la relaxine-H1 humaine illustrée sur les figures 2A et 2B, formant sa séquence C-terminale, et une partie d'une protéine procaryote formant sa séquence C-terminale.

16. Procédé d'isolement d'un gène chromosomique de relaxine, codant pour une relaxine-H1 humaine selon la revendication 15, caractérisé en ce qu'on crible une banque de gènes en employant comme sonde, une sous-unité de l'ADNc de la relaxine porcine.

17. Séquence d'ADN isolée, comprenant une séquence d'ADN codant pour la préprorelaxine-H1 humaine, la prorelaxine-H1 humaine ou la relaxine-H1 humaine, qui a été modifiée par délétion d'un ou plusieurs des codons naturels, afin de coder pour un peptide comprenant une chaîne A choisie parmi les séquences d'aminoacides de chaîne A 1—24 à 3—24, et une chaîne B choisie parmi les séquences d'aminoacides de chaîne B 1—32 à 3—23, ce peptide ayant l'activité de la relaxine-H1 humaine.

18. Séquence d'ADN isolée, comprenant une séquence d'ADN codant pour la préprorelaxine-H1 humaine, la prorelaxine-H1 humaine ou la relaxine-H1 humaine, qui a été modifiée en remplaçant un ou plusieurs des codons naturels, par des codons qui codent pour des aminoacides autres que ceux codés par le codon naturel, afin de coder pour un peptide comprenant une chaîne A choisie parmi les séquences d'aminoacides de chaîne A 1—24 à 3—24, et une chaîne B choisie parmi les séquences d'aminoacides de chaîne B 1—32 à 4—23, le résidu Met 24 de la chaîne B étant remplacé par un résidue Ala, Val, Gly ou Ser, et ce peptide ayant l'activité de la relaxine-H1 humaine.

19. Fragment d'ADN codant pour un polypeptide ayant l'activité de la préprorelaxine-H1 humaine, ce polypeptide étant choisi parmi le groupe suivant:

(a) un polypeptide ayant la séquence d'aminoacides illustrée sur les figures 2A et 2B, correspondant à la préprorelaxine-H1 humaine;

(b) un polypeptide correspondant au polypeptide (a) avec un ou plusieurs aminoacides en moins;

(c) un polypeptide correspondant au polypeptide (a) dans lequel un ou plusieurs aminoacides sont remplacés par des aminoacides différents;

(d) un polypeptide correspondant au polypeptide (a) à la séquence duquel un ou plusieurs aminoacides sont ajoutés; ou

(e) un polypeptide fusionné comprenant une séquence d'aminoacides consistant en totalité ou en partie, en la séquence d'aminoacides de la préprorelaxine-H1 humaine illustrée sur les figures 2A et 2B, formant sa séquence C-terminale, et une partie d'une protéine procaryote formant sa séquence C-terminale.

20. Fragment d'ADN codant pour un polypeptide ayant l'activité de la prorelaxine-H1 humaine, ce polypeptide étant choisi parmi le groupe suivant:

(a) un polypeptide ayant la séquence d'aminoacides illustrée sur les figures 2A et 2B, correspondant à la prorelaxine-H1 humaine;

(b) un polypeptide correspondant au polypeptide (a) avec un ou plusieurs aminoacides en moins;

(c) un polypeptide correspondant au polypeptide (a) dans lequel un ou plusieurs aminoacides sont remplacés par des aminoacides différents;

(d) un polypeptide correspondant au polypeptide (a) à la séquence duquel un ou plusieurs aminoacides sont ajoutés; ou

(e) un polypeptide fusionné comprenant une séquence d'aminoacides consistant en totalité ou en partie, en la séquence d'aminoacides de la prorelaxine-H1 humaine illustrée sur les figures 2A et 2B, formant sa séquence C-terminale, et une partie d'une protéine procaryote formant sa séquence N-terminale.

21. Fragment d'ADN isolé, codant pour un polypeptide ayant l'activité de la relaxine-H1 humaine, ce polypeptide étant choisi parmi le groupe suivant:

(a) un polypeptide ayant la séquence d'aminoacides illustrée sur les figures 2A et 2B, correspondant à la relaxine-H1 humaine;

(b) un polypeptide correspondant au polypeptide (a) avec un ou plusieurs aminoacides en moins;

(c) un polypeptide correspondant au polypeptide (a) dans lequel un ou plusieurs aminoacides sont remplacés par des aminoacides différents;

(d) un polypeptide correspondant au polypeptide (a) à la séquence duquel un ou plusieurs aminoacides sont ajoutés; ou

(e) un polypeptide fusionné comprenant une séquence d'aminoacides consistant en totalité ou en partie, en la séquence d'aminoacides de la relaxine-H1 humaine illustrée sur les figures 2A et 2B, formant sa séquence C-terminale, et une partie d'une protéine procaryote formant sa séquence N-terminale.

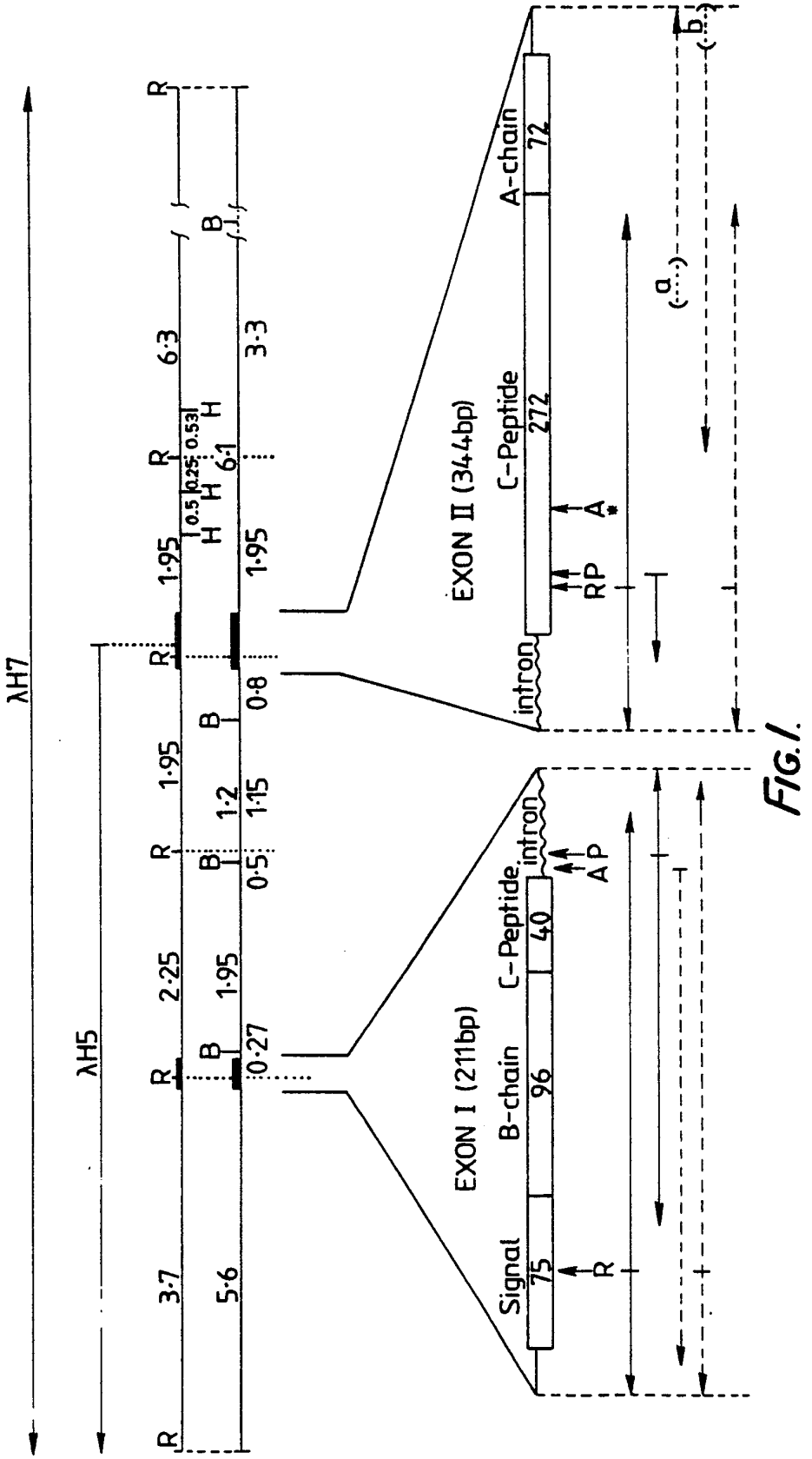

λH7
λH5
R
B
H
3·7
5·6
2·25
1·95
0·27
0·5
1·2
1·15
0·8
6·3
3·3
6·1
0·5
0·25
0·53
EXON II (344bp)
A-chain
72
C-Peptide
272
intron
R P
A
EXON I (211bp)
Signal
75
B-chain
96
C-Peptide
40
intron
A P
a
b

FIG. 1.

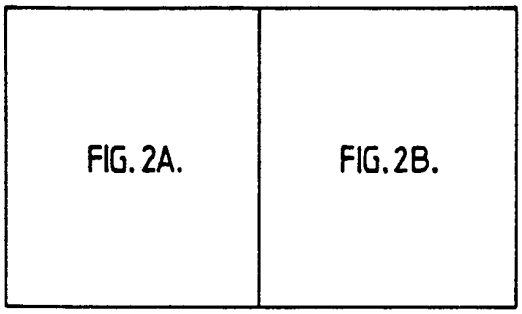


FIG. 2.

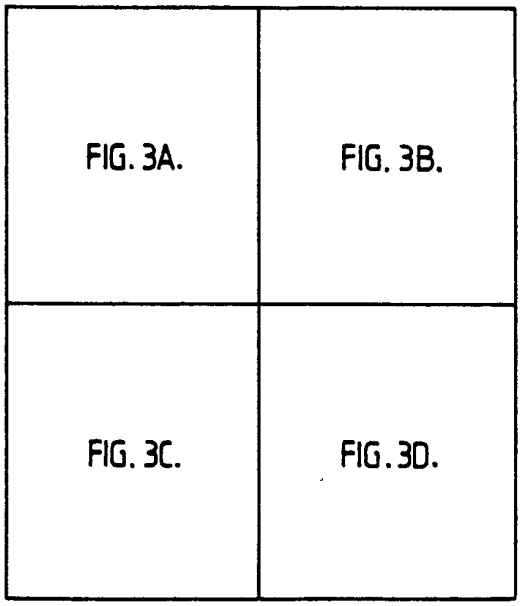


FIG. 3.


Signal Peptide
-20
Met Pro Arg Leu Phe Leu Phe His Leu Leu Glu Phe Cys Leu Leu
AUG CCU CGC CUG UUC UUG UUC CAC CUG CUA GAA UUC UGU UUA CUA
10
20
Val Ile Lys Leu Cys Gly Arg Glu Leu Val Arg Ala Gln Ile Ala
GUU AUU AAA UUA UGC GGC CGC GAA UUA GUU CGC GCG CAG AUU GCC
40
30
Asp Ala Pro Gln Thr Pro Arg Pro Val Ala Glu Ile Val Pro Ser
GAU GCU CCU CAG ACA CCU AGA CCA GUG GCA GAA AUU GUA CCA UCC
70
80
Ile Ala Asn Leu Pro Pro Glu Leu Lys Ala Ala Leu Ser Glu Arg
AUU GCU AAU UUG CCA CCG GAG CUG AAG GCA GCC CUA UCU GAG AGG
100
110
Asp Ser Asn Leu Ser Phe Glu Glu Phe Lys Lys Leu Ile Arg Asn
GAU UCC AAU CUU AGC UUU GAA GAA UUU AAG AAA CUU AUU CGC AAU
A-chain
130
140
Leu Gly Leu Asp Thr His Ser Gln Lys Lys Arg Arg Pro Tyr Val
UUA GGC UUG GAU ACU CAU UCU CAA AAA AAG AGA CGA CCC UAC GUG
160
Leu Ala Lys Tyr Cys ***
CUU GCU AAA UAU UGC UGA

FIG. 2A.

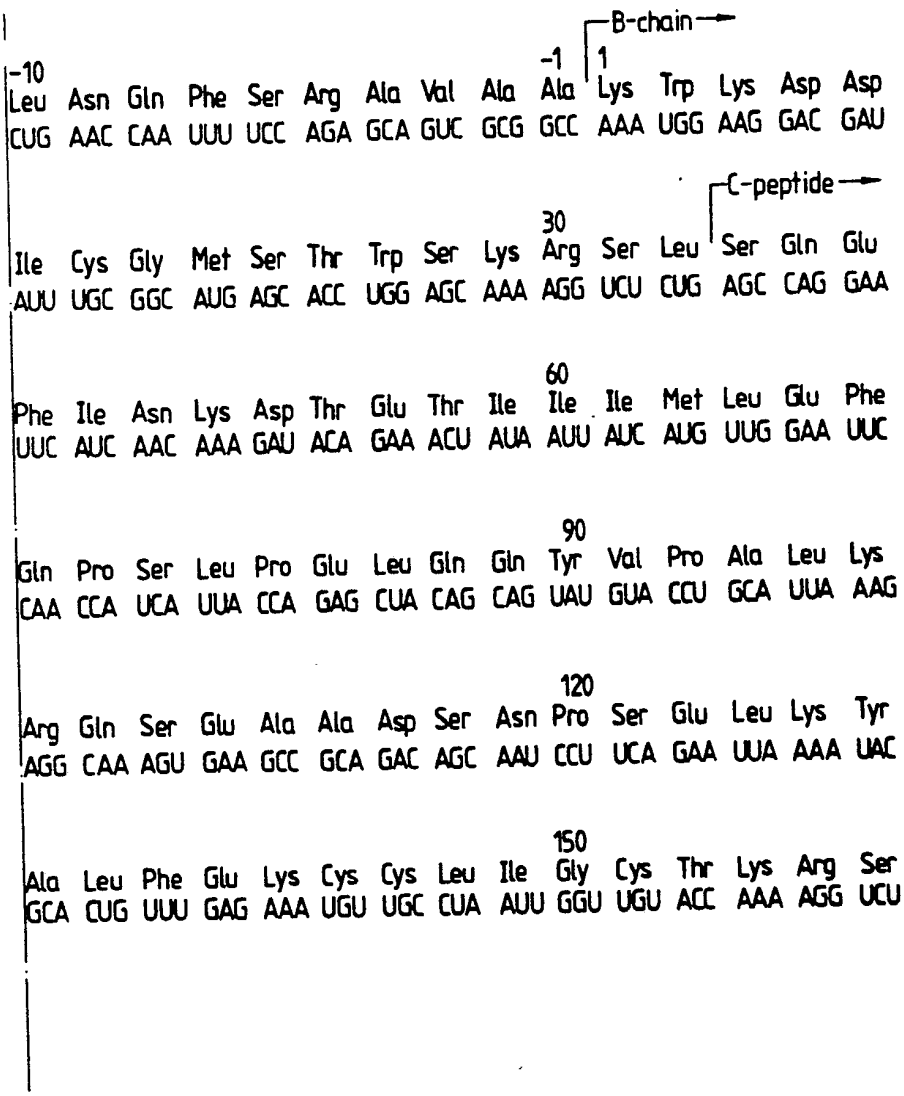

B-chain
C-peptide
-10 -1 1 30 60 90 120 150
Leu Asn Gln Phe Ser Arg Ala Val Ala Ala Lys Trp Lys Asp Asp
CUG AAC CAA UUU UCC AGA GCA GUC GCG GCC AAA UGG AAG GAC GAU
Ile Cys Gly Met Ser Thr Trp Ser Lys Arg Ser Leu Ser Gln Glu
AUU UGC GGC AUG AGC ACC UGG AGC AAA AGG UCU CUG AGC CAG GAA
Phe Ile Asn Lys Asp Thr Glu Thr Ile Ile Ile Met Leu Glu Phe
UUC AUC AAC AAA GAU ACA GAA ACU AUA AUU AUC AUG UUG GAA UUC
Gln Pro Ser Leu Pro Glu Leu Gln Gln Tyr Val Pro Ala Leu Lys
CAA CCA UCA UUA CCA GAG CUA CAG CAG UAU GUA CCU GCA UUA AAG
Arg Gln Ser Glu Ala Ala Asp Ser Asn Pro Ser Glu Leu Lys Tyr
AGG CAA AGU GAA GCC GCA GAC AGC AAU CCU UCA GAA UUA AAA UAC
Ala Leu Phe Glu Lys Cys Cys Leu Ile Gly Cys Thr Lys Arg Ser
GCA CUG UUU GAG AAA UGU UGC CUA AUU GGU UGU ACC AAA AGG UCU

FIG. 2B.

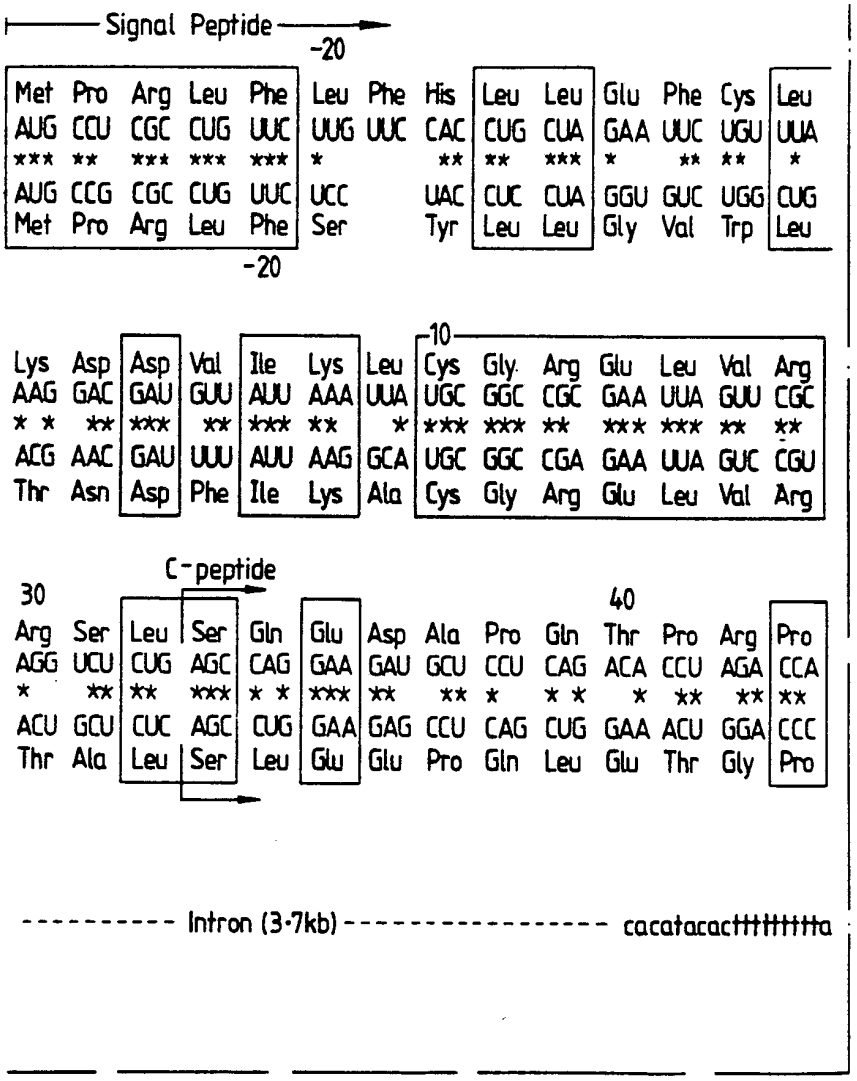

Signal Peptide
-20
Met Pro Arg Leu Phe Leu Phe His Leu Leu Glu Phe Cys Leu
AUG CCU CGC CUG UUC UUG UUC CAC CUG CUA GAA UUC UGU UUA
AUG CCG CGC CUG UUC UCC UAC CUC CUA GGU GUC UGG CUG
Met Pro Arg Leu Phe Ser Tyr Leu Leu Gly Val Trp Leu
-20
-10
Lys Asp Asp Val Ile Lys Leu Cys Gly Arg Glu Leu Val Arg
AAG GAC GAU GUU AUU AAA UUA UGC GGC CGC GAA UUA GUU CGC
ACG AAC GAU UUU AUU AAG GCA UGC GGC CGA GAA UUA GUC CGU
Thr Asn Asp Phe Ile Lys Ala Cys Gly Arg Glu Leu Val Arg
C-peptide
30
40
Arg Ser Leu Ser Gln Glu Asp Ala Pro Gln Thr Pro Arg Pro
AGG UCU CUG AGC CAG GAA GAU GCU CCU CAG ACA CCU AGA CCA
ACU GCU CUC AGC CUG GAA GAG CCU CAG CUG GAA ACU GGA CCC
Thr Ala Leu Ser Leu Glu Glu Pro Gln Leu Glu Thr Gly Pro
---------- Intron (3·7kb) ---------- cacatacacttttttttta

FIG. 3A.

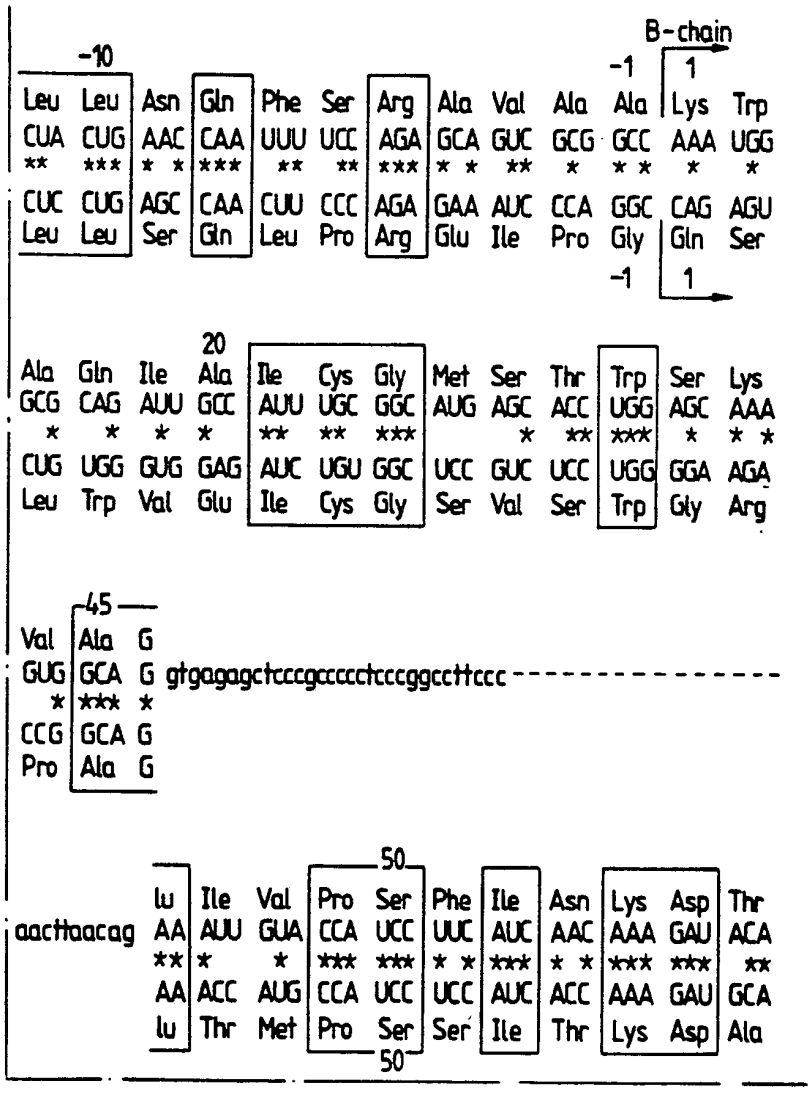

B-chain
-10
-1
1
Leu Leu Asn Gln Phe Ser Arg Ala Val Ala Ala Lys Trp
CUA CUG AAC CAA UUU UCC AGA GCA GUC GCG GCC AAA UGG
CUC CUG AGC CAA CUU CCC AGA GAA AUC CCA GGC CAG AGU
Leu Leu Ser Gln Leu Pro Arg Glu Ile Pro Gly Gln Ser
20
Ala Gln Ile Ala Ile Cys Gly Met Ser Thr Trp Ser Lys
GCG CAG AUU GCC AUU UGC GGC AUG AGC ACC UGG AGC AAA
CUG UGG GUG GAG AUC UGU GGC UCC GUC UCC UGG GGA AGA
Leu Trp Val Glu Ile Cys Gly Ser Val Ser Trp Gly Arg
45
Val Ala G
GUG GCA G gtgagagctcccgccccctcccggccttccc
CCG GCA G
Pro Ala G
50
lu Ile Val Pro Ser Phe Ile Asn Lys Asp Thr
aacttaacag AA AUU GUA CCA UCC UUC AUC AAC AAA GAU ACA
AA ACC AUG CCA UCC UCC AUC ACC AAA GAU GCA
lu Thr Met Pro Ser Ser Ile Thr Lys Asp Ala
50

FIG. 3B.

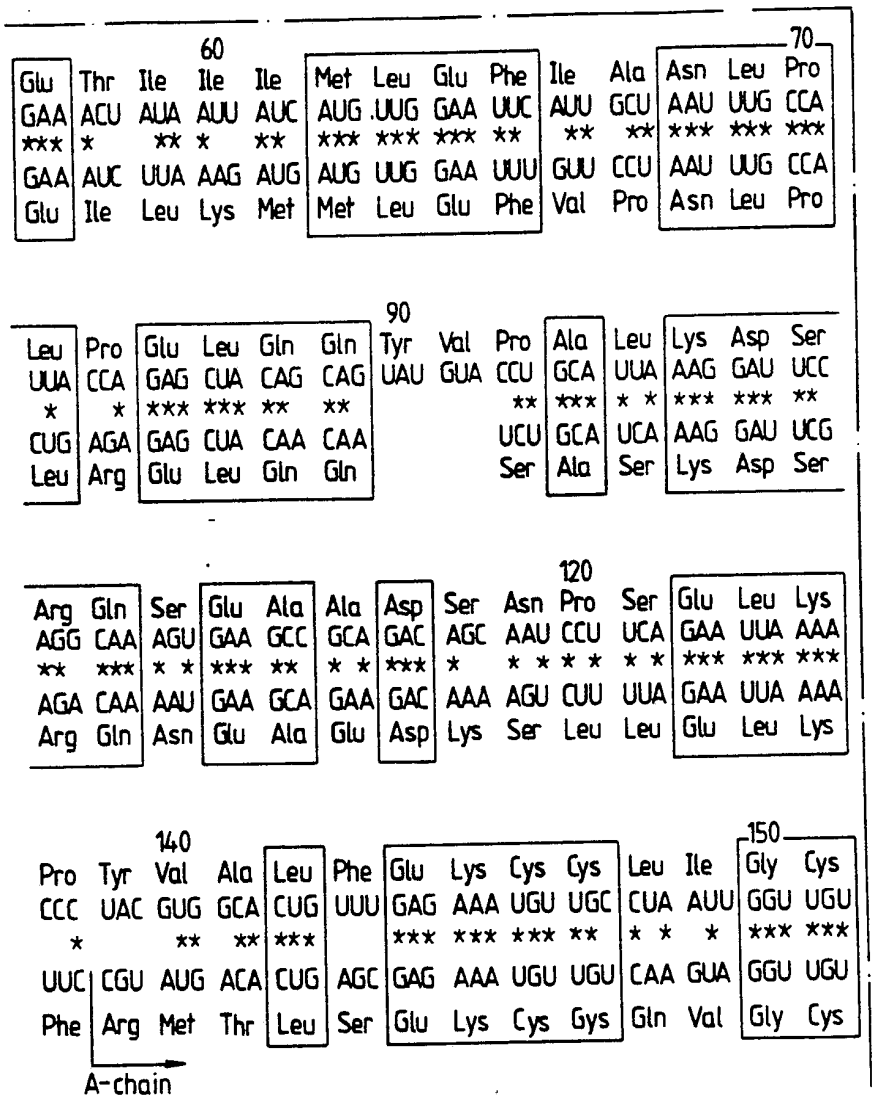


FIG. 3C.

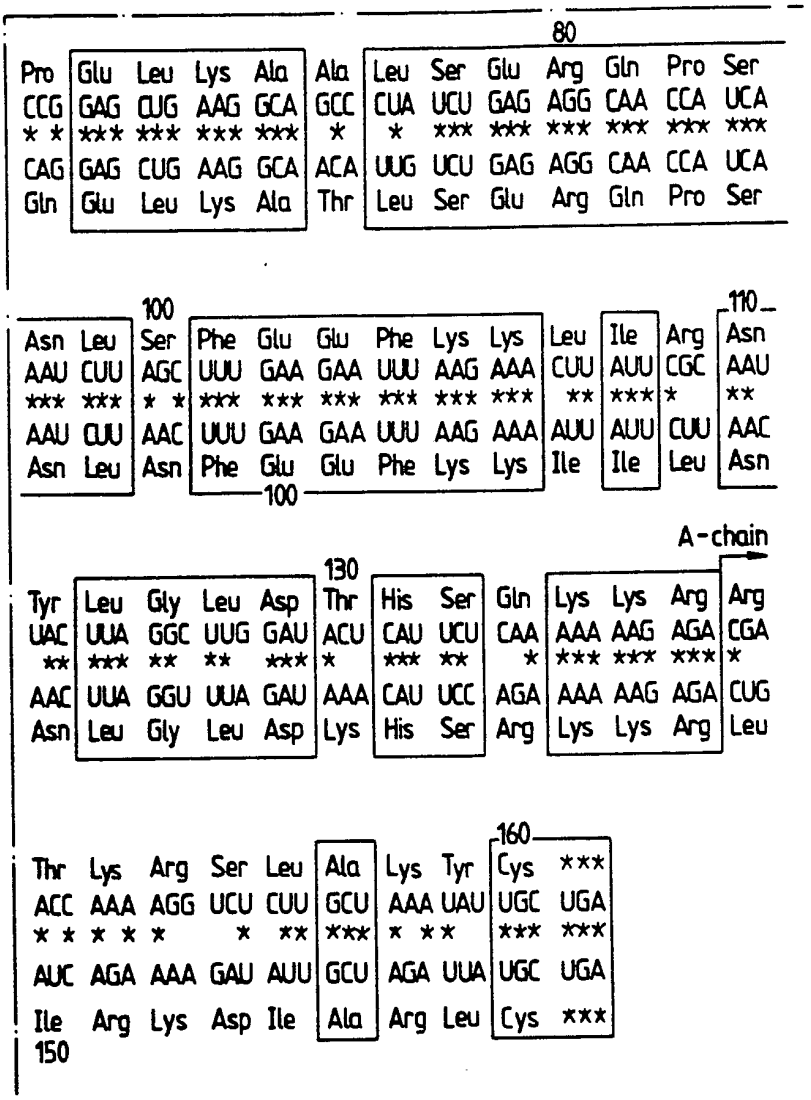

80
Pro Glu Leu Lys Ala Ala Leu Ser Glu Arg Gln Pro Ser
CCG GAG CUG AAG GCA GCC CUA UCU GAG AGG CAA CCA UCA
CAG GAG CUG AAG GCA ACA UUG UCU GAG AGG CAA CCA UCA
Gln Glu Leu Lys Ala Thr Leu Ser Glu Arg Gln Pro Ser
100
Asn Leu Ser Phe Glu Glu Phe Lys Lys Leu Ile Arg Asn
AAU CUU AGC UUU GAA GAA UUU AAG AAA CUU AUU CGC AAU
AAU CUU AAC UUU GAA GAA UUU AAG AAA AUU AUU CUU AAC
Asn Leu Asn Phe Glu Glu Phe Lys Lys Ile Ile Leu Asn
100
110
A-chain
130
Tyr Leu Gly Leu Asp Thr His Ser Gln Lys Lys Arg Arg
UAC UUA GGC UUG GAU ACU CAU UCU CAA AAA AAG AGA CGA
AAC UUA GGU UUA GAU AAA CAU UCC AGA AAA AAG AGA CUG
Asn Leu Gly Leu Asp Lys His Ser Arg Lys Lys Arg Leu
160
Thr Lys Arg Ser Leu Ala Lys Tyr Cys ***
ACC AAA AGG UCU CUU GCU AAA UAU UGC UGA
AUC AGA AAA GAU AUU GCU AGA UUA UGC UGA
Ile Arg Lys Asp Ile Ala Arg Leu Cys ***
150

FIG. 3D.

DOCUMENT 5

23.3.88/pc

Datum/Date
23. 11. 87

Zeichen/Ref/Réf	Anmeldung Nr./Application No./Demande n°//Patent Nr./Patent No./Brevet n°
Fb 691	83307553.4- 2.1.05

Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire
HOWARD FLOREY INSTITUTE OF EXPERIMENTAL PHYSIOLOGY AND MEDICINE

Please give the complete applicatic number i all com- municatic

Communication pursuant to Article 96(2) and Rule 51(2) EPC

The /further/ examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(1) EPC.
You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a **period**

of four **months**

from the notification of this communication, this period being computed in accordance with Rules 78(3) and 83(2) and (4) EPC.

Amendments to the description, claims and drawings are to be filed where appropriate within the said period in **three copies** on separate sheets (Rule 36(1) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Article 96(3) EPC).

Note: where objection is raised on grounds of lack of unity (Article 82 EPC). 26 NOV 1987

If, for the purpose of rectifying lack of unity, the application is **limited** within the period laid down in the communication and the applicant intends to file a divisional application in respect of the subject-matter affected by the limitation, the said divisional application must be filed **with the EPO** at The Hague or in Munich within **two months** at the latest of **limitation** being effected (receipt of the document) (Rule 25(1) (b), Article 76(1) EPC; see EPO Guidelines C-VI, 9.2). No separate communication concerning this time limit is envisaged.

R Galijani
L. Galligan

Primary examiner
for the Examining Division

Enclosures: 3 page/s reasons (Form 2044/2906)

Telephone numbers:

Primary examiner (substantive examination) (089) 2399- 2763

Formalities officer (Formalities including extension of time limits) (089) 2399- 2420

Examiners' clerk (other matters) (089) 2399- 2151

Registered letter

The examination is being carried out on the **following application documents** (description, claims and, where appropriate, drawings):

[X] the application documents as published

[ ] description, pages ....., as published
description, pages ....., filed with your letter of .....
description, pages ....., filed with your letter of .....
description, pages ....., filed with your letter of .....

[ ] claims, Nos. ....., as published
claims, Nos. ....., filed with your letter of .....
claims, Nos. ....., filed with your letter of .....
claims, Nos. ....., filed with your letter of .....

[ ] drawings, sheet/fig. ....., as published
drawings, sheet/fig. ....., filed with your letter of .....
drawings, sheet/fig. ....., filed with your letter of .....
drawings, sheet/fig. ....., filed with your letter of .....

[X] with the amendments, suggested in your letter of ...5.08.87....., to the description/ the claims/ the drawings

1. The amendments suggested in your letter dated 5.8.87 to Claims 2, 4, 6 are allowable under Rule 88 EPC.

2. The Examining Division concurs with the objection put forward by the Search Division as to lack of unity (Article 82 EPC). However, in the opinion of the Examining Division not only two, but three separate inventions are claimed in the present application, namely:

a) Claims 1 to 23 which relate to methods and means for the production of human H2-relaxin and its precursors by recombinant DNA technology;

b) Claims 24 to 29 and partially Claims 30 to 32 which deal with human H2-relaxin analogues and to their production method;

c) Claims 30 to 32 (partially) which deal with a method

.../...

for preparing human H2 relaxin based on the chemical combination of the different chains.

Rule 30 EPC lists different categories of independent claims which are permitted to coexist in one and the same European patent application in order to satisfy the unity requirements of Article 82 EPC.

When taking the sets of Claims a), b) and c) into consideration, it is clear that sets b) and c) relate to further technical aspects or developments with respect to set a) and that, therefore, they should be made subject of separate parallel applications.

Set a) already includes a plurality of independent claims directed to methods and means for the production of synthetic human H2 relaxin and its precursors. The plurality of independent claims which are allowed to coexist, although being directed to products and methods of different nature (cf. for example, DNA sequences, expressed proteins, vectors, transformed cells) nevertheless all relate to one solution to the same technical problem.

The inventions of sets b) and c), although having partially as starting point the invention of group a), nevertheless concern other technical problems or aspects and are therefore to be considered as non-unitary.

3. The matter disclosed in the present application is new with respect to the European Search Report (Article 54 EPC). Moreover, since the finding of a specific alternative form of human relaxin and of its precursors (relaxin H2 and prepro-pro-forms) can be considered unexpected in view of the prior art, the matter of the present application, appears to be patentable under Article 52(1) EPC.

4. However, before a patent can be granted, the claims should be properly drafted in order :

a) to clearly identify in terms of technical features the matter to be protected (Article 84, Rule 29(1) EPC) and

b) to avoid embracing known (Article 54 EPC) or obvious matter (Article 56 EPC).

In this respect it is observed that, in the absence of specific structural features or parameters, the designation H2 per se as used in the various claims is meaningless because a distinction between the H1 and H2 forms of relaxin (or their precursors) and between the H1/H2 relaxins and the known human relaxin merely on the basis of the biological activity is not possible. In fact the activity is identical for all forms of relaxin. Moreover, since admittedly the H1 form of EP-A-101 309 and the H2 form of the present application display not only the same activity, but also a considerable degree of homology (see figure 2), the expressions "or a subunit thereof", "or an equivalent of such a gene or subunit" used in the claims are objectionable not only under Article 84 (lack of clarity), but also under Articles 54 (3),(4) (lack of novelty). You are therefore kindly requested to redraft the claims in terms of the true technical features which characterize the invention and which clearly and unambiguously distinguish it from known or conflicting matter. In particular, the matter claimed in the present application must be clearly distinguishable from the matter of the earlier European patent application quoted above (in this respect reference is made also to the communication dated 03.08.88 in said case and to the prior art cited therein).

It is observed, for example, that present Claims 8-9 and Claims 7-8 of said application relate to the same process (identical procedural steps).

5. You are requested to file new claims which take account of the above comments.

DOCUMENT 6

Businesses predict chaos over Europe's data rules

Elisabeth Geake

BUYING an international airline ticket or using a credit card outside Europe could be illegal if a draft European law is implemented as it stands. The draft directive on data protection was attacked repeatedly at a conference in London last week for being unworkable, contradictory and so badly worded that even lawyers were uncertain of its meaning.

Like Britain's Data Protection Act, the proposed European legislation is supposed to safeguard the interests of individuals by controlling who can keep what information about whom. Its aim is to bring the safeguards up to the same standard throughout the European Community.

When the single European market comes into force at the end of this year, citizens will be encouraged to move between member states and will consequently appear on computer records in more than one country. Businesses will want to use lists of existing and potential customers in several countries. And when controls at national borders within the Community are removed, customs, immigration and police services will share data.

The draft directive came under fire from British officials and executives at last week's conference organised by the business information company IIR. Wanda Goldwag, director for foreign exchange for the Thomas Cook group, pointed out how badly the draft is worded. "This is an appalling piece of legislation and was obviously got out in a hurry," she said.

Britain's existing legislation allows most data to be transferred abroad, but the directive will prevent this unless there is a good reason, or the recipient is in a country with similar laws. This would hit any company doing business outside Europe—possibly even those which use only paper records, as the draft covers some of those too.

Lawyers are advising companies that from the end of this year it could be illegal to pass information on plane tickets out of Europe, making international bookings impossible. Credit-card and banking transactions could be illegal, as could direct marketing and mailshots beyond the Community's borders.

According to John Mogg, a senior official at the European Commission responsible for internal markets, the proposed law is intended to prevent "data havens" forming outside Europe in countries with no data protection laws. But Goldwag says it would be better to penalise those who abuse the system rather than make the law quite so restrictive. This is also the view of the Home Office in Britain.

Companies in the Third World which offer contract data processing are already suffering. NDL International is a London company which distributes and processes 3 million questionnaires a year on consumer preferences. Before the draft directive was published, all the answers were typed into computers in Barbados. Tony Coad, the managing director, described his 105-strong workforce as "the most committed you could hope to meet".

But in the light of the draft, Coad has "decided it would be unsafe to continue operating there", and he has moved the operation to Barnsley.

Francis Aldhouse, the deputy to Britain's Data Protection Registrar, welcomes the increased protection of privacy that the draft promises, but disagrees with many of the other provisions. For example, on sensitive data, he says "it seeks to impose prohibitions beyond what is practical". Under the draft, criminal convictions, for instance, may not be held in private.

The European Parliament will discuss the directive later this month. It is supposed to be finalised by the end of the year. But Goldwag warns: "When a draft begins this badly, it takes ages to sort it out." □

Greens go to law to block human gene patent

THE Green group in the European Parliament has appealed against the granting of a patent for a human gene. Last year the European Patent Office in Munich awarded the Howard Florey Institute at the University of Melbourne, Australia, a patent on the gene for a human hormone, relaxin. The Greens have lodged a formal protest with the EPO in the hope that the case will arouse public pressure for a European ban on patenting human genes.

Relaxin, a hormone that causes the muscles of the birth canal to relax, is produced by the ovaries during labour. Relaxin from pigs has been used to assist women in labour. Genentech, the US-based biotechnology firm, has taken out a licence for relaxin with a view to marketing the human version as an obstetric drug.

Genentech will have to wait for patent protection in Europe, however. The legal procedure started by the Greens last week takes time. An appeal against the first European patent on a genetically modified plant, granted in 1989, could finally be heard by the appeal board of the EPO later this year.

The Greens have launched the case in order to delay the licence, says their legal counsel, Rolf Wilhelms. They hope public pressure against patenting human genes will be brought to bear on the EPO while the appeal is pending. They also want to force changes to the directive on patents for biological inventions, to be decided by the European Community this year ("Europe debates the ownership of life", *New Scientist*, 4 January).

The EPO has granted patents on several human genes, starting with the insulin gene in the mid-1980s. The European directive, as it stands, would permit other human genes to be patented. The Greens say genes should not be patentable, because they are discoveries, not inventions.

Rainer Osterwalder of the EPO says genes are regarded as "chemical compounds that can be used to provide technical solutions to precisely defined problems". It is the production and application of the cloned gene that is regarded as the patentable invention, he says, not the discovery.

The patenting of human material is causing increasing strife in Europe. The Baylor College of Medicine in Texas applied to the EPO in 1988 to patent a method for expressing specific genes in the mammary glands of mammals. They also applied to patent any mammal with the implanted gene in its germ line. The application asked separately for a patent on "mammals" and "nonhuman mammals". The EPO says Baylor wanted to patent a human with the implanted gene, and rejected the application. Baylor is appealing. Paul Braendli, head of the EPO, says "human beings are not patentable".

But patenting humans is not explicitly prohibited in European law. Braendli bases his assertion on his interpretation of an article of the European Patent Convention stating that patents must not contravene "public order". This moral concept has so far been a matter for interpretation by the patent examiners.

The Greens want the European directive on biological patents to make morality explicit. They want to stir up public pressure to ensure that Community industry ministers ban patenting of human genes specifically, when they make the final decision on the directive. Debora MacKenzie, Brussels

Spaceplane finds friends despite official delay

HEADS of four European aerospace companies last week signed an agreement to create Euro-Hermespace, a corporation to develop the European spaceplane Hermes. Unfortunately for the signatories, member states of the European Space Agency have still not decided to proceed with the Hermes project.

The French companies Dassault and Aerospatiale hold 51·6 per cent of stock in the new corporation. Deutsche Aerospace holds 33·4 per cent and Italy's Alenia 15 per cent. In a move which looks like an attempt to draw Hermes's harshest critic, Germany, fully into the venture, the president of Euro-Hermespace's supervisory board has been named as Johann Schäffler, deputy head of Deutsche Aerospace.

The future of the spaceplane was to have been decided by ministers meeting in Munich last November, but because of escalating costs and a lack of money they postponed the go-ahead for another year. A decision is now expected at the end of this year.

Director-general of the new corporation, Philippe Couillard of the French firm Aerospatiale, warned that the Hermes programme could not proceed without some long-term investment before the final decision. "Investment implies future commitments. We can no longer say we are getting on with the programme if we do not invest, but our investment choices will be prudent ones," he said. Sylvia Hughes, Paris

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 112 149 B1**

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **10.04.91**

(51) Int. Cl.5: **C12N 15/16**, C12P 21/02, C07K 13/00, C07K 7/00

(21) Application number: **83307553.4**

(22) Date of filing: **12.12.83**

Divisional application 88110103 filed on 24.06.88.

(54) Molecular cloning and characterization of a further gene sequence coding for human relaxin.

(30) Priority: **13.12.82 AU 7247/82**

(43) Date of publication of application:
27.06.84 Bulletin 84/26

(45) Publication of the grant of the patent:
10.04.91 Bulletin 91/15

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

(56) References cited:
EP-A- 0 068 375
EP-A- 0 086 649
EP-A- 0 101 309

TELEGEN TECHNICAL FEATURE, 82000533, abstract 31808, 1982, Environment Information Center, New York, US;H. NIAL:"Hormones and genetic engineering";paper presented at the Genetic Engineering Symposium in Sydney, November 18-20, 1981

(73) Proprietor: **HOWARD FLOREY INSTITUTE OF EXPERIMENTAL PHYSIOLOGY AND MEDICINE**
c/o University of Melbourne
Parkville Victoria(AU)

(72) Inventor: **Hudson, Peter John**
1 Sefton Street
Bulleen Victoria(AU)
Inventor: **Niall, Hugh David**
3 Bendigo Avenue
Elwood Victoria(AU)
Inventor: **Tregear, Geoffrey William**
62 Hawthorn Grove
Hawthorn Victoria(AU)

(74) Representative: **Brown, John David et al**
FORRESTER & BOEHMERT Widenmayerstrasse 4/I
W-8000 München 22(DE)

EP 0 112 149 B1

NATURE, vol. 291, May 14, 1981, pp. 127-131; Macmillan Journals Ltd., Basingstoke, GB; P. HUDSON et al.:"Molecular cloning and characterization of cDNA sequences coding for rat relaxin."

DNA, vol. 1, no. 2, 1982, pp. 155-162; Mary Ann Lieber Inc., New York, US; J. HALEY et al.:"Porcine relaxin: Molecular cloning and cDNA structure"

NATURE, vol. 301, no. 5901, February 17, 1983, pp. 628-631; Macmillan Journals Ltd., Basingstoke, GB; P. HUDSON et al.:"Structure of a genomic clone encoding biological active human relaxin"

NUCLEIC ACIDS RESEARCH, vol. 11, no. 19, 1983, pp. 6597-6609; IRL Press, Ltd., Oxford, GB; A STEWART et al.:"Cloning and expression of a porcine prorelaxin gene in E. coli"

NATURE, vol. 267, June 9, 1977, pp. 544-546; Macmillan Journals Ltd., Basingstoke, GB; R. JAMES et al.:"Primary structure of porcine relaxin: Homology with insulin and related growth factors"

Description

This invention relates to the molecular cloning and characterization of a gene sequence coding for human relaxin. The invention is also concerned with recombinant DNA techniques for the preparation of human relaxin, prorelaxin and preprorelaxin.

In our Australian Patent Application No. 17906/83 (PF 5352/82, filed 12th August, 1982) (EP-A-0101309), we described the molecular cloning and characterization of a gene sequence coding for human relaxin. We have now found a second gene which also codes for human relaxin.

More specifically, this invention relates to an isolated and purified (i.e.,"cloned") human gene coding for prorelaxin, preprorelaxin, and the A and/or B and/or C peptide chains of human relaxin, methods for isolating and purifying the genes and a method for transferring the genes to and replicating the genes in a host cell. The cloned genes are expressed by the host cell when fused with a host-expressable prokaryotic or eukaryotic gene. The genes are thus useful in the production of human relaxin for therapeutic purposes.

The invention also relates to the peptides human relaxin, prorelaxin and preprorelaxin, to the individual peptide chains which comprise these sequences and to modified forms of these peptides.

The invention further relates to modified genes coding for the individual relaxin chains and for the above-mentioned modified forms.

[Note: References used in the following description are collected at the end of the description.]

Pioneering work by Hisaw (1926) suggested an important role for the peptide hormone relaxin in mammals through its effects in dilating the pubic symphysis, thus facilitating the birth process. Relaxin is synthesized and stored in the corpora lutea of ovaries during pregnancy and is released into the blood stream prior to parturition. The availability of ovaries has enabled the isolation and amino acid sequence determination of relaxin from pig (James et al, 1977; Schwabe et al, 1977) rat (John et al, 1981) and shark (Schwabe et al, 1982). The biologically active hormone consists of two peptide chains (known as the A and B chains) held together by disulphide bonds, two inter-chain and one intra-chain. The structure thus closely resembles insulin in the disposition of disulphide bonds which has led to speculation of a common ancestral gene for these hormones (James et al, 1977; Schwabe et al, 1977).

Recombinant DNA techniques have been applied to the isolation of cDNA clones for both rat and porcine relaxins (Hudson et al, 1981; Haley et al, 1982), see also Australian Patent Application No. 11834/83 (PF 2695/82) (=EP-A-0086649). Synthetic undecamer nucleotides, prepared on the basis of amino acid sequence information, were used as primers for the synthesis of cDNA probes greatly enriched in relaxin cDNA sequences which identified relaxin cDNA clones in libraries derived from both rat and porcine ovarian tissue. The relaxin structural gene was found to code in both cases for a single chain precursor which resembles preproinsulin in the overall configuration, i.e., signal peptide/B chain/C peptide/A chain.

In our Application No. 17906/83 (EP-A-101309) we described the use of probes based on the C peptide region of porcine relaxin to select out a relaxin gene from a human genomic library. This approach resulted in the successful identification of a genomic clone which we have now designated "H1" from which the structure of the entire coding region of a human preprorelaxin was determined.

The present invention arises from a continuation of the work described in Application No. 17906/83 (EP-A-101309) in which we sought to confirm the gene structure described in that application. We have investigated cDNA clones in libraries derived from ovarian tissue from pregnant human females using as a probe a segment of the previously identified human H1 gene corresponding to approximately 300 nucleotides of the C peptide/A-chain coding region (amino acids 64-161). Positive cDNA clones were isolated and sequencing of these revealed a cDNA sequence which was not identical with the sequence previously established and which coded for a form of preprorelaxin different to that described in our earlier application.

We have also isolated from the human genomic library described in our copending Australian Patent application No. 17906/83 (PF 5352/82) (=EP-A-0101309) a recombinant phage containing exon 1 of the H2 gene where exon 1 comprises the coding region of the signal, B-peptide, and part of the C-peptide similar to that of the H1-gene.

It is now believed that either or both the presently-described gene which we have designated "H2" and the "H1" gene described in our Application No. 17906/83 (=EP-A-0101309) expressed in human reproductive tissue, for example ovary and placenta, and/or other tissues including but not limited to gut, brain and skin, since both genes express peptides with relaxin-like activity.

The corpora lutea of the ovary as well as decidual and placental tissues are the most likely sites for expression of relaxin-related genes. However, in view of the wide distribution of many peptide hormones it is highly likely that the relaxin gene is also expressed in non-reproductive tissues, including brain and the gastrointestinal tract. Relaxin has the general properties of a growth factor and is capable of altering the

nature of connective tissue and influencing smooth muscle contraction. We believe that one or both of the gene structures described in this specification and that of Application No. 17906/83 (EP-A-101309) to be widely distributed in the body. we suggest that the relaxin peptides expressed from these genes will play an important physiological role in addition to their well documented hormonal function during reproduction.

The following abbreviations are used in this description.

H1 - the relaxin gene described in Application No. 17906/83 (EP-A-0101309), being deduced from a genomic clone.

H2 - the relaxin gene described herein, being deduced from a cDNA clone.

DNA - deoxyribonucleic acid	A - Adenine
RNA - ribonucleic acid	T - Thymine
cDNA - complementary DNA (enzymatically synthesized from an mRNA sequence)	G - Guanine
	C - Cytosine
	U - Uracil
mRNA - messenger RNA	

The coding relationships between nucleotide sequence in DNA and amino acid sequence in protein are collectively known as the genetic code, which is set out below.

First position (5'end)	Second position U	C	A	G	Third position (3' end)
U	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	Stop	Stop	A
	Leu	Ser	Stop	Trp	G
C	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu	Pro	Gln	Arg	G
A	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val	Ala	Glu	Gly	G

The abbreviations used for the amino acids in the table are identified as follows.

Phenylalanine	(Phe)	Histidine	(His)
Leucine	(Leu)	Glutamine	(Gln)
Isoleucine	(Ile)	Asparagine	(Asn)
Methionine	(Met)	Lysine	(Lys)
Valine	(Val)	Aspartic acid	(Asp)
Serine	(Ser)	Glutamic acid	(Glu)
Proline	(Pro)	Cysteine	(Cys)
Threonine	(Thr)	Tryptophan	(Try)
Alanine	(Ala)	Arginine	(Arg)
Tyrosine	(Tyr)	Glycine	(Gly)

Each 3-letter codon represented in the table, e.g., AUG, CAU (otherwise known as a nucleotide triplet) corresponds to a trinucleotide of mRNA, having a 5'-end on the left and a 3'-end on the right. The letters stand for the purine or pyrimidine bases forming the nucleotide sequence. All DNA sequences given herein are those of the strand whose sequence corresponds to the mRNA sequence, with thymine (T) substituted for uracil (U).

The invention will be further described and elucidated in the following discussion. Reference will be

made to the accompanying drawings in which:

Figure 1 : shows an abbreviated restriction map and sequencing strategy for the cDNA clone in pBR322, genomic clone H11, and GT10 cDNA clones a-f. Arrows indicate the direction of sequencing on end-labelled fragments (see methods). GT10 clones a-f were sequenced by subcloning into an M13 vector as described hereinafter. Nucleotides are numbered from the AUG initiation codon, position 1-3, to the termination codon, position 554-556.

Figure 2 : compares the amino acid and mRNA sequence of human preprorelaxin H2 (upper) with the corresponding H1 (lower) sequence. The sequences have been aligned to maximize homology with nucleotide identities being indicated by asterisks and amino acid homologues by boxed-in areas. Amino acids are numbered from the start of the B-chain (H2 gene sequence starting at -1 and H1 sequence at +1) although this position represents only the hypothetical start of the B chain sequence and has been deduced simply from the homology to the related porcine arid rat preprorelaxin structures. The asterisk beneath Ala 45 in the C peptide denotes the position of an intron in the G/CA codon in both genes.

Figure 3: autoradiographs of identical nitrocellulose strips taken from either a) Northern gel transfer of human ovarian RNA or b) λplaques corresponding to the H1 gene (λH7) or H2 gene (λGT10-a) using as hybridization probes A: a random primed 600 bp H2 relaxin cDNA fragment (72-660), B: H2-specific 25 mer (483-507), C: H1-specific 25 mer (483-507), D: H1-specific 25 mer (248-272).

Figure 4 autoradiographs of identical nitrocellulose strips following Northern gel transfer of human ovarian RNA using as hybridization probes fragments of the H2 cDNA clone in pBR322 (see Figure 1).

A: 600 bp fragment (72-660) corresponding to most of the coding region
B: 5' untranslated region (to Hinf I site at nucleotide 30)
C: 3' untranslated region (from Hinf I site at nucleotide 660)
D: 3' untranslated region (from Hpa I site at nucleotide 850)

Figure 5: comparison of the amino acid sequences of the B and A chains between the two human relaxin genes, human insulin, and other members of the relaxin family. Boxed areas highlight residue which are conserved between the two human relaxin genes-and the relaxin family. Arrows indicate probable sites of proteolytic cleavage with confirmation by protein sequencing data of the amino terminal residue of the B and A chains of porcine (Schwabe et al, 1977; James et al, 1977), rat (John et al, 1981), shark (Schwabe et al, 1982) and dogfish relaxins (Schwabe et al, 1983).

The H2 mRNA sequence shown in Figure 2 was determined by the methods described hereinafter. For ease of comparison, the numbering of the amino acids previously used for the peptide derived from the H1 sequence has been maintained in the present description of the H2-derived peptide. The structure of H1-preprorelaxin was deduced from the genomic sequence by comparison with the homologous structures of pig and rat relaxin. The H2-preprorelaxin structure was deduced by comparison with the H1 structure as well as the pig and rat structures. Confirmation of the A and B peptide chain structures has been provided by synthesis and chain recombination in vitro which produces a material which is biologically active in the uterine contraction assay.

It will be seen from Figure 2 that the present and previous sequences show significant differences as well as similarities. Notable are:

(1) Significant amino acid differences in three main areas:
  (a) the N-terminus of the B-chain
  (b) the N-terminus of the A-chain
  (c) the middle of the C-peptide.
(2) Regions of strong homology in the B-chain and C-peptide:
  (a) 120 identical bases from Val^{6} to Ile^{47}.
  (b) 88 - 90 identical bases from Phe^{101} to Ser^{132}.

The two genes are therefore very similar but the differences are sufficient to indicate that the H2- gene is indeed a second gene and not simply a polymorph of H1.

The mode of in vitro processing of the H1 preprorelaxin is not yet fully known but by analogy with pig relaxin, cleavage of the signal peptide would be expected to occur at the Ala^{-1} -Lys^{1} bond. Similarly excision of the H1-C peptide is predicted to occur at Leu^{32} - Ser^{33} and Arg^{136} - Arg^{137}, thus giving the H1-B and H1-A chains or respectively 32 and 24 residues (Figure 2).

In H2 preprorelaxin Ala^{1} has been replaced by Asp and so we would predict cleavage of the signal peptide after the alanine corresponding to position -2 in H1. Cleavage at the H2-B chain/C peptide junction is expected after Leu^{32} by analogy to all other prorelaxins, thus leaving the H2-B chain with 33 residues. Cleavage at the H2-C peptide/A chain junction would occur after Arg^{136} by analogy to rat preprorelaxin, thus leaving the H2-A chain with 24 residues.

As noted in our studies on pig relaxin, there are core sequences in the pig relaxin B and A chains which

contain all the essential elements for biological activity. Our synthetic studies on the human relaxin chain show similar results, as set out in more detail hereinafter.

According to one aspect of the present invention, there is provided a gene for the expression of human H2-preprorelaxin.

Except where otherwise specified, all following references to the gene sequences for preprorelaxin, prorelaxin, relaxin and the signal, A, B and C peptides, and to the peptides themselves will be understood to refer to the H2 variants and to exclude the H1 variants.

More specifically, this aspect of the invention provides a double-stranded DNA fragment for the expression of human preprorelaxin, which comprises a coding strand and a complementary strand corresponding to the complete mRNA (codons -25 to 160) sequence shown in Figure 2 of the accompanying drawings.

The invention also includes any sub-unit of the H2-preprorelaxin gene sequence described herein, or any equivalent of the said sequence or sub-unit. Among the sub-units to be included by this statement are the individual structural genes coding for the signal peptide chain and the separate H2-A and H2-B peptides and the H2-C chain of human preprorelaxin (see Figure 2) and any combinations of these chains, e.g., the genes for expressing the H2-A and H2-B peptides, separately or as prorelaxin (with the H2-C chain). The sub-units also include fragments and combinations of fragments of any of said gene sequences.

Thus according to another aspect of the present invention, there is provided a gene for the expression of human prorelaxin.

More specifically, this aspect of the invention provides a double-stranded DNA fragment for the expression of human prorelaxin, which comprises a coding strand and a complementary strand corresponding to the codons numbered as-1 to 160 of the mRNA sequence shown in Figure 2 of the accompanying drawings.

According to a further aspect of the present invention, there are provided genes for the separate expression of the A, B and C chains of human relaxin or any combination of two or more of the said chains and any fragment or combination of fragments of the said chains.

More specifically, this aspect of the invention provides double-stranded DNA fragments for the separate expression of the A and/or B and/or C chains of human relaxin (or fragments as described above) which comprise a coding strand and a complementary strand corresponding to the codons numbered -1 to 32, 33 to 136 and 137 to 160 of the mRNA sequence shown in Figure 2 of the accompanying drawings.

The genes described above in addition to the codons specified may also include the appropriate "start" and "stop" codons, e.g., AUG and UGA respectively (codons -25 and 161 in Figure 2).

Those skilled in the art will appreciate that polymorphic forms of the genes may exist. Such forms are included in the present invention.

The invention further includes the complements of the above sequences, sub-units or equivalents, and the corresponding RNA sequences, sub-units or equivalents.

According to another aspect of the present invention there is provided a DNA transfer vector comprising the deoxynucleotide sequences corresponding to the genes defined above.

As shown above, the genetic code contains redundancies, that is certain amino acids are coded for by more than one codon. Thus the invention includes deoxynucleotide sequences in which the codons depicted in the drawings, or their cDNA equivalents are replaced by other codons which code for the same amino-acid.

Furthermore, as already indicated above, peptides with relaxin activity may be produced which differ from the B and/or A chain structures of natural relaxin. Such differences may involve deletion of one or more amino acids and/or addition of further amino acids and/or substitution of different amino acids in the natural chains.

Thus the invention also includes genes and DNA transfer vectors as described above wherein one or more of the natural codons are deleted and/or are replaced by codons which code for amino acids other than that coded by the natural codon, and/or further codons are added to the natural sequence.

The transfer vectors of the invention may also include inter alia , genetic information which ensures their replication when transferred to a host cell. Such cells may include, for example, the cells or prokaryotic microorganisms, such as bacteria, yeasts and moulds, and also eukaryotic cells, including mammalian cells and cell lines.

Examples of transfer vectors commonly used in bacterial genetics are plasmids and the DNA of certain bacteriophages. Both phage DNA and bacterial plasmids have been used as the transfer vectors in the present work. It will be understood however, that other types of transfer vectors may be employed. The general techniques of forming such transfer vectors and transforming them into microorganisms are well known in the art.

The invention also includes a prokaryotic or eukaryotic cell transformed by any of the transfer vectors described above.

One preferred microorganism is the very familiar Escherichia coli , but any other suitable microorganism may be used.

According to a still further aspect of the present invention, there is provided a process for making a DNA transfer vector for use in maintaining and replicating a deoxynucleotide sequence coding for human preprorelaxin, characterised by ligating a deoxynucleotide sequence coding for human preprorelaxin with a DNA molcule prepared by cleaving a transfer vector with a restriction enzyme.

DNA transfer vectors for use in maintaining and replicating deoxynucleotide sequences coding for human prorelaxin and for the A and B chains of human relaxin may be similarly prepared from the appropriate deoxynucleotides.

The A and B peptide chains, and also prorelaxin and preprorelaxin may be prepared by the usual process of gene expression, that is by growing cells containing the appropriate transformed transfer vector and isolating and purifying the required peptide(s) produced by the cells.

Thus, the invention further includes a process for making a fusion protein comprising the amino acid sequence of human preprorelaxin as its C-terminal sequence and a portion of a prokaryotic or eukaryotic protein as its N-terminal sequence, characterised by incubating a cell culture transformed by an expression transfer vector comprising a deoxynucleotide sequence coding for human preprorelaxin, prepared in accordance with the process described above.

Fusion proteins comprising the amino acid sequences for human prorelaxin and/or the A and/or B and/or C chains of human relaxin may be similarly prepared.

The fusion peptide products thus produced will be in the form of a fusion protein in which the desired peptide is linked with a portion of a prokaryotic or eukaryotic protein characteristic of the host cell. Such fusion proteins also form a part of this invention.

The invention also includes a process for synthesizing human prorelaxin comprising the A and B peptides separated from each other by a C peptide, characterised by incubating a culture of cells, transformed by an expression transfer vector comprising a deoxynucleotide sequence coding for said human prorelaxin, prepared as described above, under conditions suitable for expression of said sequence coding for human prorelaxin, and purifying human prorelaxin from the lysate or culture medium of said cells.

The peptide of interest can be recovered from the fusion product by any suitable known cleavage procedure.

As already indicated above the transfer vector may be modified by codon substitution /deletion/addition and such modifications will give rise to modified fusion peptides. In this way appropriate modifications may be made to facilitate the cleavage of the fusion peptides, for example, at the junction of B/C or C/A chains or to modify the peptide chain behaviour during subsequent chemical or biological processing.

As indicated above, the invention also provides human relaxin, prorelaxin and preprorelaxin.

Relaxin may be prepared by direct combination of the separate A and B chains by any of the procedures currently known and used for the preparation of insulin.

Also in a similar manner to insulin, relaxin may be prepared from prorelaxin by oxidizing or otherwise converting the sulfhydryl groups on the A and B peptides of relaxin, prepared as described herein, to form disulfide crosslinks between said A and B peptides, and then excising the C peptides, for example, by an enzyme-catalyzed hydrolysis specific for the bonds joining the C peptide to the A and B peptides.

Accordingly, the present invention further provides a method for the synthesis of human relaxin which comprises combining the A and B chains of relaxin (in their full-length, shortened or modified forms) by methods known per se for combination of A and B chains of human insulin.

One such method comprises reducing a mixture of the S-sulphonated A and B chains and then allowing the mixture to oxidize in air.

We have also found that the efficiency of the above procedure is improved when one or both of the A and B chains is in the form of an S-thioethyl-cys derivative rather than the S-sulpho form.

In our Australian Patent Application No. 15413/83 (PF 4385/82) we also showed that one or both of the A and B chains of relaxin can be shortened at the amino and/or carboxy terminii without significant loss of biological activity and with improved combination yields. These techniques apply equally to the preparation of human relaxin.

Another aspect of the invention provides a human relaxin analogue consisting essentially of shortened and/or modified forms of the natural B and/or A peptide chains.

This aspect of the invention also provides a method for producing a human relaxin analogue which comprises the step of forming the shortened and/or modified B and/or A peptide chains and combining

them by any of the methods described above. These latter aspects are dealt with in the Divisional application nr. 88110103 published as EP-A-0303033.

Our investigations with both pig and human relaxin (H1) show that relaxin activity may be present with human A chains as short as A(10-24) and B chains as short as B(10-22) although the expected practical minima are respectively A(4-24) and B(4-23). The synthetic pig peptide A(4-24)-B(1-25) is already known to have relaxin activity.

In general, for the present relaxin structure (H2) the A chain can be varied from A(1-24) to A(10-24) and B chain from B(-1-32) to B(10-22).

The preferred combinations are derived from:

A		B
(1-24)		(-1-23)
any of (2-24)	with any of	(up to)
(3-24)		(-1-32)

Modifications of the B and/or A chains, in accordance with the present invention may involve either "genetic" modification, as described above, or chemical modification of the B and/or A chains (in either full-length or shortened form) prior to combination by the method of the invention. Two types of modification may be employed, either singly or in combination.

The first type involves the modification of one or more of the amino-acids which occur in the natural or shortened B and/or A chains. Such modification will generally involve protection of active groups on one or more of the amino-acids by methods known per se , and the protecting groups may, if desired, be removed after combination of the (modified) A and B chains.

Examples of this type of modification include the acetylation, formylation or similar protection of free amino groups, including the N-terminal, amidation of C-terminal groups, or the formation of esters of hydroxyl or carboxylic groups. The formyl group is a typical example of a readily-removable protecting group.

The second type of modification includes replacement of one or more of the natural amino-acids in the B and/or A chains with a different amino acid (including the D-form of a natural amino-acid). This general type of modification may also involve the deletion of a natural amino-acid from the chain or the addition of one or more extra amino-acids to the chain.

The purpose of such modifications is to enhance the combination yields of the A and B chains, while maintaining the activity of the product, i.e., relaxin or an analogue thereof, or to enhance or modify the activity of the product for a given combination yield. Such modification may extend to the production of synthetic analogues which have relaxin-blocking or -antagonistic effects.

A specific example of the first type of modification is the modification of the tryptophan (Trp) residue at B2 by addition of a formyl group.

Examples of the second type of modification are replacement of the Met moiety at B24 with norleucine (Nle), valine (Val), alanine (Ala), glycine (Gly), serine (Ser) or homoserine (HomoSer).

The invention in this aspect also includes human relaxin analogues formed from natural or shortened B and/or A chains modified in accordance with the invention as described above.

The A and B peptide chains, and also prorelaxin and preprorelaxin may be prepared by the usual process of gene expression, that is by growing a microorganism containing the appropriate transformed transfer vector and isolating and purifying the required peptide(s) produced by the microorganism.

The peptide products thus produced may be in the form of a fusion protein in which the desired peptide is linked with a portion of a prokaryotic protein

The invention is further described and illustrated by the following description of the experimental procedures used and the results obtained thereby.

Methods and Materials

Messenger RNA isolation and cDNA cloning

Human ovarian tissue obtained during surgery for the treatment of an ectopic pregnancy was quickly frozen on dry ice and the RNA isolated in 5M guanidinium thiocyanate (Merck) according to the method of Chirgwin et al ., 1979. Poly-A^+ RNA was converted into double stranded DNA (Wickers et al, 1978) and cloned either by the homopolymeric G/C tailing method into a pBR322 plasmid vector (Chang et al., 1978) or by the lambda packaging method using the λGT10 vector (Huynh et al., 1983). In our experience the efficiency of transformation with the pBR322 method (10^4 recombinants/μg of cDNA) was far less efficient than the lambda technique (up to 10^5 recombinants/μg of cDNA).

Preparation of hybridization probes

Radiolabelled probes were prepared by primed synthesis on various DNA fragments using denatured random primers of calf thymus DNA (Hudson et al., 1983, Taylor et al., 1976). The DNA template (100-200 ng) was denatured with the random primers (1 μg) by boiling in 20 μl of water for 2 minutes. Synthesis was initiated by the addition of a 30 μl reaction mixture containing 50mM Tris-HCl pH 8.0, 50- NaCl, 1mM DTT, 10mM $MgCl_2$, 5 units of E. coli DNA Polymerase 1 (Klenow fragment), 500 μM each of dCTP, dGTP, dTTP and 0.3 μM a-[^{32}P]-dATP (Approx. 3000 Ci/mmol, Amersham). After incubation at 37° C for 30 minutes the reaction was terminated by dilution into 300 μl of a buffer containing 0.3M NaCl, 10mM Tris-HCl, pH 8.0, 1mM EDTA and passed through a Sephadex-G50 column, (1cm x 5cm) in the same buffer. The radiolabelled probe was collected from the peak fractions at void volume and precipitated with 2 volumes of ethanol at -20° C for 2 hours using tRNA (10 μg) as carrier.

Selection of specific cDNA clones

To screen the human ovarian cDNA clone bank for relaxin specific sequences we used as a probe a segment of the previously identified human H1 gene corresponding to a 400 nucleotide segment coding for the C peptide and A-chain from amino acid 64, through the termination codon and including 80 bases of the 3' untranslated region. A single positive cDNA clone from the pBR322 library was isolated and sequenced. 23 unique recombinants were isolated from the λGT10 libraries, but of these only 6 were subjected to complete nucleotide sequence analysis.

DNA sequence analysis

The sequencing strategy and an abbreviated restriction map of the cDNA clones are summarized in Figure 1. The recombinant plasmid in pBR322 was digested with restriction enzymes Hpa II (P), Hinf I (F) or Taq I (T) and end-labelled using reverse transcriptase and the appropriate α-labelled deoxynucleotide triphosphate (dCTP for Hpa II, and Taq I, dATP for Hinf I). Fragments were cleaved internally with a second restriction endonuclease and then separated by electrophoresis on 8% polyacrylamide gels prior to sequencing by the chemical degradation method of Maxam and Gilbert et al, 1977.

cDNA clones in λGT10 were sequenced by subcloning Eco R1 restriction fragments into M13mp9 and employing the techniques described by Sanger et al, (1980).

Southern and Northern gel analyses

Performed on purified genomic DNA after restriction endonuclease cleavage by the method of Southern (1975) or on purified RNA. The DNA fragments which were used as probes were found to be specific for either exon I or exon II of the H1 genomic clone despite having a small amount of flanking sequences. These fragments were generated by subcloning into M13mp8 a 500 bp Alu I fragment of the λH7 clone in the case of the exon I probe, or a 400bp Eco RI-Ava II fragment for the exon II probe. A probe from the H2 cDNA clone was generated by digesting with Hinf I and isolating a 300 bp doublet corresponding to the coding region from Asp 1 to the termination codon and including 110 bases of the 3' untranslated region (Figure 1). Oligonucleotide probes were synthesized by the phosphite chemistry method of Beaucage and Caruthers (1981) and were end-labelled with γ-^{32}P-ATP using T4 polynucleotide kinase. Hybridization conditions were calculated on the basis of the G + C content.

Isolation and nucleotide sequence analysis of the H2 genomic clone

The human genomic lambda library of Lawn et al (1978) was screened by method described earlier (Hudson et al, 1983) except that a mixture of DNA fragments corresponding to exons I and II of the H1 genomic clone was used for the probe as described above. Positive phage were grown in litre scale liquid cultures, the DNA isolated and digested with restriction endonucleases prior to mapping with the exon I and II probes. A 4 kilobase EcoRI fragment was found to contain the entire exon I coding region which differentiated this clone from the homologous H1 gene structure. This fragment was subcloned into M13mp8 and sequenced by the technique of Maxam and Gilbert (1977). After digesting with Ava I, fragments spanning the coding region were end-labelled and cleaved internally by a second restriction enzyme (Hpa II of Hinf I) to generate fragments suitable for sequence analysis.

Isolation of a cDNA clone

Samples of human corpus luteum were made available to us as a result of surgical intervention in ectopic pregnancies or from lutectomy at the time of Caesarian section. From the RNA isolated from a single corpus luteum a cDNA library was constructed in pBR322 providing about 300 unique recombinants. Screening this library with an H1-cDNA probe revealed a single recombinant with sequence homology to human relaxin I. To increase the total number of recombinants from such small amounts of ovarian tissue we constructed cDNA libraries using the λGT10 cloning system (Huynh et al , 1983). Screening with a relaxin-specific probe identified 23 unique cDNA clones of which six were characterized as shown in Figure 1. Nucleotide sequence analysis revealed that all 6 cDNA recombinants encoded fragments of the same relaxin structural gene (Figure 2), yet this sequence was different to the genomic clone reported earlier (Hudson et al., 1983). We expected that this novel sequence corresponded to the second human relaxin gene (H2) which had been observed in genomic DNA.

Surprisingly, none of the cDNA clones contained a polyadenosine sequence at the 3' end, although the size of cDNA clones in PBR322 and λGT10 (1800 bp and 1900 bp respectively) indicate that large transcription products were being synthesized during the cloning procedure. These two cDNA clones had overlapping sequence identity at the 3' terminus confirming that they were derived from the same mRNA structure. We attributed the loss of the poly-A tail either to premature termination of the double-stranding transcription reaction or to excessive S1 nuclease degradation during the cloning procedure.

Isolation of a genomic clone corresponding to the second gene

A thorough screen of 10^8 recombinant phage from the human genomic library of Lawn et. al., (1978) using mixed probes specific for exon I or II of the λH7 relaxin clone revealed 16 positive phage. Small scale restriction mapping analysis revealed that 14 of these recombinant phage corresponded to the H1 relaxin gene reported earlier (11 were identical to the λH7 genomic clone; 3 were identical to λH5 a different genomic clone of the H1 gene as previously reported by Hudson et. al., 1983). However, the other 2 recombinant phage were identical and had a unique restriction pattern characteristic of the H2 relaxin gene whose structure is given in Figure 1. The unusual ratio of recombinants reflects either their proportion in the original genomic library or results from selective growth during amplification. Southern blot analyses of this new recombinant phage (λH11) using separate probes corresponding to either exon I or II of the λH7 clone, revealed that λH11 contained only the exon I coding region. Attempts to find a full length genomic clone corresponding to the H2 relaxin gene either in the library of Lawn et. al. (1978) or in another library (Dr. R. Crawford, unpublished) have so far been unsuccessful.

The nucleotide sequence of the relaxin coding region of λH11 was found to be identical to that observed in the cDNA clone shown in Figure 2. An intron interrupts the coding region in exactly the same position as in the λH7 genomic clone (Hudson et. al., 1983) suggesting that these genes arose by a gene duplication event at some point in evolution.

Northern gel analysis

RNA was isolated from several samples of human corpora lutea taken from different individuals during surgical intervention for ectopic pregnancy or during Caesarian section operations. Northern gel analysis

using probes made from the coding region of either relaxin gene revealed that two major mRNA species of approximate sizes 1000 bp and 2000 bp were present in five human ovarian RNA samples tested (Figure 3). The smaller mRNA species were 2-3 fold more abundant in the RNA samples tested and this result was independent of whether the probe used in the analysis corresponded to H1 or H2 relaxin indicating that high cross-hydridization rates occur under our experimental conditions. To differentiate whether these two mRNA species represent the separate products of the H1 and H2 genes, oligonucleotide probes were synthesized over a region of minimum homology (60%) between the two relaxin genes (residues 137-144 in Figure 2). These synthetic 25 mers were radiolabelled by kinasing with γ-^{32}P-ATP and used as hybridization probes under conditions shown to provide specificity for either the H1 or H2 gene (Figure 3). Northern gel analysis using these radiolabelled probes revealed that both mRNA species corresponded to products of the H2 gene. We could not detect any transcription products from the H1 gene using the specific probes, although low level expression (less than 5% of the H2 level) would have been difficult to identify.

To analyse the different mRNA transcripts from the H2 gene, we made specific probes from segments of the two large H2 cDNA clones corresponding to the coding region and 5' and 3' untranslated regions (Figure 4). The larger mRNA transcript (approximately 2kb in length) selectively hybridized to segments of the 3' untranslated region from both cDNA clones, from a position approximately 100 bases from the termination codon. A potential polyadenylation signal exists in the nucleotide sequence of the cDNA clones, 140 bases from the termination codon, and this region does have homology to the porcine relaxin polyadenylation site. However, the question of whether the shorter mRNA product is polyadenylated near this position cannot be resolved until full length cDNA clones corresponding to both mRNA forms have been isolated and characterised.

In the absence of the genomic sequence of the H2 gene it is impossible to define the mechanisms leading to the formation of the two mRNA transcripts. It is possible, like the collagen and β-microglobulin genes, that cleavage of the primary RNA transcript could occur at alternative polyadenylation sites. On the other hand we cannot rule out the possibility of alternative splicing mechanisms such as occurs in the calcitonin, growth hormone and α-crystallin genes.

The primary structure of preprorelaxin encoded by the H2 gene

The mode of in vivo processing of the human preprorelaxin genes is not yet fully understood and has to be deduced by analogy to the processing of porcine and rat preprorelaxins (Figure 5). The predicted B and A chain structures for the H1 and H2 genes have been aligned to other members of the relaxin family and human insulin in Figure 5.

Cleavage of the signal peptide in H1 has been predicted (Hudson et al., 1983) to occur after a short side chain residue such as Ala^{-1}, -2 or -4 or after Ser-6. Cleavage after Ala-1 is consistent with the homology to porcine preprorelaxin and human preproinsulin. Similarly, cleavage of the H2 signal peptide probably occurs after Ala-2 by such analogy, although cleavage after Ala-4 or Ser-6 are other possibilities.

By analogy to rat and pig prorelaxins, cleavage at the B chain/C peptide junction would occur after Leu 32 in both H1 and H2 precursors. However, both human relaxin B chains possess at positions 29-30 the conserved dibasic sequence Lys-Arg, which is a known processing site in other prohormones such as proinsulin, and cleavage here cannot be excluded. Direct amino acid sequence analysis of relaxin isolated from corpora lutea of pregnancy will be required to settle this point. In the meantime it seems that the most likely structure of the H1 B chain would be 32 residues in length (Lys 1 to Leu 32) and the H2 B chain would be 33 residues (Asp-I to Leu 32).

Cleavage at the C peptide/A chain junction of H1 prorelaxin has been predicted (Hudson et al., 1983) to occur after Arg 136 within a group of 4 basic residues because the Arg-Pro imide bond at 137-138 would be resistant to proteolysis. H2 prorelaxin has the same sequence of 4 basic residues and a similar processing step after Arg 136 would result in both the H1 and H2 relaxin A chains being 24 residues in length.

Biological Activity of the H2 gene

As noted in earlier studies on synthetic pig relaxin peptides, there are core sequences in the pig relaxin B and A chains which contain all the essential elements for biological activity. Our synthetic studies on the H1 relaxin peptides has shown that combination of the complete H1 A chain (Arg 137-CYS 160) to a shortened form the H1 B chain (Lys 1-Ser 25) produced material which possessed biological activity

(Hudson et al., 1983). Further studies on both the H1 and H2 gene structures using peptide synthesis reveals that both genes code for forms of relaxin which are biologically active in the rat uterine contractility assay.

Chemical Synthesis of a modified human relaxin H2 (hRLX) A(1-24) - B(-1-24)

(i) Synthesis of human relaxin A-chain, H2 hRLX A(1-24)

The amino acid sequence corresponding to residues 1 to 24 of the human relaxin A-chain, deduced as described above from the nucleotide sequence of the cDNA clone, was synthesized by the solid-phase procedure according to the general principles described by Merrifield (e.g. Barany, G. and Merrifield, R.B. In "The Peptides". Ed. E. Gross & J. Meienhofer, Academic Press, N.Y., pp. 1-284, 1980).

N-α-tertiarybutyloxycarbonyl* -4-methylbenzyl-L-cysteine (*hereinafter "BOC") was coupled to a 1% crosslinked polystyrene resin via the phenylacetamidomethyl (PAM) linkage to a level of 0.30 mmole/gm using the method of Tam et al., (Synthesis 12 , 955-957, 1979). The BOC-L-CYS-PAM resin (8.0 gm) was transferred to the reaction vessel of a Beckman Model 990 Peptide Synthesizer and the amino acid sequence from residues 23 through to 1 was assembled by the stepwise addition of each suitably protected amino acid. The amino terminal BOC protecting group of each amino acid was removed by treatment of the resin with 35% trifluoroacetic acid in methylene chloride for 30 minutes followed by neutralization with 5% diisopropylethylamine in methylene chloride for 15 minutes. After each treatment the resin was washed thoroughly with methylene chloride. The next amino acid in the sequence (suitably-protected at the α-amino with the BOC group and where necessary with the side-chain functional group appropriately protected) wad coupled to the resin using dicyclohexylcarbodiimide (DCC). The resin was stirred with the amino acid in methylene chloride for 10 minutes prior to the introduction of the DCC which was also dissolved in methylene chloride. A 2.5 molar excess (6.0 mmole) of amino acid and DCC was used for each coupling. After stirring for 1 hour a sample of the resin was removed from the reaction mixture and tested for the presence of free amino groups using the ninhydrin procedure of Kaiser et al. (Anal. Biochem., 34 , 595-598, 1970). If the ninhydrin test was negative indicating complete coupling the reaction cycle was continued with BOC deprotection, neutralization and coupling of the next amino acid. For a positive ninhydrin test the coupling reaction was repeated with further amino acid and DCC.

Amino acids with side-chain functional groups were used as the following protected derivatives: N-α-BOC-2,6-dichlorobenzyl-L-tyrosine, N-α-BOC-ε -chlorobenzyloxycarbonyl-L-lysine; N-α-BOC-L-serine O-benzyl ether; N-α-amyloxycarbonyl-N^G-tosyl-L-arginine; N-α-BOC-L-threonine O-benzyl ether; N-α-BOC-S-ethyl mercapto-L-cysteine (for CYS at A-chain sequence position 15, 11 and 10).

Following the assembly of the 1-24 peptide sequence, the final BOC group on the amino terminal arginine was removed using the deprotectdion neutralization cycle and the peptide-resin dried in vacuo (wt of peptide resin 13.0 gm). A portion of the peptide-resin (2 gm) was treated with anhydrous hydrogen fluoride in the presence of anisole (2 ml) at 0 ° C for 30 minutes. The total time for contact of the resin-peptide with hydrogen fluoride (HF) was kept to a minimum (not more than 70 minutes) by rapid removal of the HF under oil-pump vacuum. The resin-peptide was then washed several times with ethyl acetate to remove excels anisole, the peptide extracted into 1M acetic acid and the solution lyophilized. The yield of crude peptide, (with the cysteines at positions 10, 11 and 15 still protected as the S-thioethyl derivative) was 392 mg. Initial purification of the crude peptide was by gel-filtration on Biogel P10 in 0.1M acetic acid. The fractions representing the major peak from this column, which eluted at a position corresponding to a molecular weight of approximately 3000, were collected and lyophilized. Amino acid analysis of a sample of this peptide indicated that all the amino acids of the 1-24 sequence were present in the correct ratio.

Further purification of the [S-thioethyl $Cys^{10,11,15}$]-hRLX A (1-24) peptide was affected by preparative reverse-phase HPLC on a Waters C-18 Bondapak column using a 0.1% TFA-water/acetonitrile solvent system.

A sample (80 mg) of the peptide purified by gel-filtration was S-sulfonated with a mixture of sodium sulfite and sodium tetrathionate (total reaction time of 3 hours) according to the method described by Du et al., (Scientia Sinica, 101, 84-104 (1961)). The precipitate which formed during the S-sulfonation reaction was removed by filtration and both the precipitate and the supernatant solution dialyzed against distilled water at 4 ° C for 48 hours. The contents of the dialysis bags were lyophilized to yield 39.5 mg of peptide from the supernatant solution and 20.3 mg of peptide from the precipitate which occurred during

the S-sulfonation reaction. A sample of the 'soluble' [S-sulfo $Cys^{10,11,15,24}$] hRLX A(1-24) peptide was purified by preparative reverse-phase HPLC on a Waters C-18 Bondapak column using a 0.1% TFA-water/acetonitrile solvent system.

(ii) Synthesis of shortened human relaxin B-chain, H2 hRLX B(-1-24)

The amino acid sequence corresponding to residues -1 to 24 of the H2 human relaxin B-chain was synthesized using the procedures described above and commencing with 6.0 gm N-α-tertiarybutyloxycarbonyl-L-methionine-O-benzyl-L-serine-phenylacetamido-methyl polystyrene resin with a loading of 0.5 mmole Met per gm. The side-chain protecting groups used in the A-chain synthesis were also employed for the B-chain including the S-ethyl mercapto derivative for both cysteines at positions 10 and 22. The glutamic acid residues at positions 4 and 5 and the aspartic acid residue at -1 were added as the N-α-BOC-benzyl ester derivative. The glutamine at position 18 was coupled by the active ester procedure using N-α-BOC-L-glutamine-p-nitrophenyl ester in DMF. Following coupling or the tryptophan at position 2, 0.1% indole was added to the trifluoroacetic acid deprotecting reagent and to the subsequent methylene chloride washes.

The final weight of peptide-resin after removal of the BOC group from the amino terminal aspartic acid residue and vacuum-drying was 8.5 gm. A portion of the peptide resin (3.5 gm) was treated with anhydrous hydrogen fluoride in the presence of anisole (2 ml) at 0 °C for 30 minutes and the B-chain peptide isolated using the procedure described above for the A-chain. The crude [S-thioethyl $Cys^{10,22}$] hRLX B(-1-24) (0.97 gm) was purified by gel filtration on BioGel P10 in 1M acetic acid followed by preparative HPLC.

A sample (100 mg) of the peptide purified by gel filtration was S-sulfonated at pH 8.3 for 3 hours, the reaction mixture filtered and the precipitate and supernatant solutions dialyzed against distilled water. The 'soluble' peptide recovered after lyophilization was 42.4 mg; the 'insoluble' peptide was 59.5 mg. The S-sulfonated B-chain peptides were further purified by preparative HPLC using a C-18 reverse-phase column and 0.1% TFA-water-acetonitrile solvent system.

(iii) Chain Combination

The synthetic H2 hRLX A(1-24) and H2 hRLX B(-1-24) peptides were combined using the procedure described by Chance and Hoffmann (Australian Patent Application No. 68844/81) for insulin chains wherein the S-sulfonated peptides were mixed in a ratio of A : B of 2.6: 1 at a peptide concentration of 10 mg/ml in glycine buffer pH 10.5. Dithiothreitol in glycine buffer was then added in an amount to give a total of 1.0 sulfhydryl groups for each S-sulfo group. The reaction mixture was then stirred in an open vessel for 24 hours.

As a further modification to this procedure we have found that the chain combination reaction to form biologically active relaxin proceeded efficiently when one or preferably both of the peptide chains are used as their S-thioethyl-Cys derivatives rather than in the S-sulfo form specified by Chance and Hoffmann (op.cit.) in the case of insulin. The use of S-thioethyl Cys peptides eliminates a reaction and purification step required to convert the peptides to the S-sulfo derivatives. In our experience the S-sulfonation reaction of relaxin peptides is accompanied by side reactions which render the S-sulfo peptides difficult to purify resulting in low yields.

Using the above conditions chain combination yields from 1.5 to 6.0% have been achieved as measured by biological activity in the rat uterine contractility assay of Wiqvist & Paul (Acta Endocrinol., 29, 135-136, 1958).

Example of Chain Combination Reaction

Human relaxin H2 [S-thioethyl $Cys^{10,11,15}$] A(1-24) (4.2 mg dry wt., 2.4 mg peptide by amino acid analysis, 0.84 μmole) was dissolved in 500 μl of 0.1M glycine buffer pH 10.5 in a 3 ml stoppered plastic centrifuge tube. Human relaxin H2 [S-sulfo $Cys^{10,11}$] B(-1-24) (1.60mg, 1.60 mg peptide by amino acid analysis, 0.33 μmole) dissolved in 200 μl of 0.1M glycine buffer pH 10.5 was added and the mixture agitated. An aliquot (23.0 μl, 2.21 μmole DTT) of a stock solution of dithithreitol (DTT) made up in 0.1 M glycine buffer pH 10.5 (0.96 μmole DTT in 10 ul) was added to the peptide solution and following a brief agitation the reaction mixture was allowed to stand at 4 °C for 24 hours open to the air. The mixture was then centrifuged and aliquots of the supernatant solution tested for relaxin biological activity in the rat uterine contractility assay. Aliquots of the reaction mixture inhibited the spontaneous contractions of the rat uterus in a dose-related manner. A 75 μl aliquot completely inhibited uterine contractions equivalent to a chain combination yield of 5.3% as compared to a native pig relaxin A22 B31 standard.

Synthesis of authentic human relaxin H2 : hRLX A(1-24) - B(-1-32)

(i) Synthesis of full length H2 human relaxin B-chain :hRLX B(-1-32)

The amino acid sequence corresponding to residues -1 to +32 of the full length H2 human relaxin B-chain was synthesised using the procedures described above and commencing with 6.4 gm N-α-tertiarybutyloxycarbonyl-L-leucine phenyl acetamido methyl polystyrene resin with a loading of 0.23 mmol Leu per gm. The side-chain protecting groups used for the A(1-24) and B(-1 - 24) peptides were also employed for the full length B-chain including the S-ethyl mercapto derivative for both cysteines at positions 10 and 22. A modification of this strategy was the use of the N-formyl derivative of BOC-L-tryptophan for coupling at sequence positions 27 and 2.

The final weight of the peptide-resin following chain assembly was 8.2gm. A portion of the peptide resin (4.0gm) was treated with anhydrous hydrogen fluoride-anisole as described in previous examples to yield 1.50gm of crude [S-thioethyl $Cys^{10,22}$, N-formyl $Trp^{2,27}$] hRLX B(-1 - 32). The crude peptide was purified by gel filtration on BioGel P6 in 0.1M acetic acid. The major peaks eluting from the gel filtration column were characterised by amino acid analysis. The fractions with analyses consistent with the -1 to +32 peptide sequence were collected and lyophilised. Deformylation of the tryptophan residues was effected by treating the peptide (100mg) with sodium hydroxide solution (5ml) pH 11.5 for 5 min. during which time the peptide precipitated from solution. The reaction mixture was neutralised to dissolve the peptide and applied directly to a BioGel P6 column in 0.1M acetic acid. Removal of the formyl groups from tryptophan was monitored by UV spectroscopy by following the disappearance of the N-formyl absorption at 300 nm and the appearance of the characteristic tryptophan spectra with an absorption maximum at 280 nm. Peptide fractions eluting from the column with the correct amino acid anlysis were collected and lyophilised.

Attempts to further purity the [S-thioethyl $Cys^{10,22}$] hRLX B(-1 - 32) peptide by preparative HPLC were not successful because of loss of peptide by adsorption to the column media. Peptide purified by gel chromatography was used directly in chain combination experiments.

(ii) Chain combination of A(1-24) with B(-1 - 32) : preparation of human relaxin H2

The synthetic S-sulfonated and S-thioethyl H2 human relaxin A(1-24) peptides were coupled to S-thioethyl H2 human relaxin B(-1 -32) using the same chain combination procedures described previously for the shortened B-chain (-1 - 24). Samples of the recombination mixture were tested for relaxin biological activity in the rat uterine contractility assay. Aliquots of the reaction mixture inhibited the spontaneous contractions of the rat uterus in a dose-related manner. A 100µl aliquot completely inhibited uterine contractions equivalent to a chain combination yield of 3.0% as compared to a native pig relaxin A22 B31 standard.

The features disclosed in the foregoing description, in the following claims and/or in the accompanying drawings may, both separately and in any combination thereof, be material for realising the invention in diverse forms thereof.

References

Anderson, M.L., Long, J.A. and Hayashida, T. Immunofluorescence studies on the localisation of relaxin in the corpus luteum of the pregnant rat. Biol. Reprod. 13 , 499-504 (1975).

Beaucage, S.L. and Caruthers, M.H. Tetrahedron Lett. 22 , 1859-1862 (1981).

Chang, A.C.Y. Nature 275 , 617-624 (1978).

Chirgwin, J.M., Przybyla, A.E., MacDonald, R.J. and Rutter, W.J., Isolation of biologically active ribonucleic acid from sources enriched in ribonuclease. Biochem. 18 , 5294-5299, (1979).

Haley, J., Hudson, P., Scanlon, D., John, M., Cronk, M., Shine, J., Tregear, G. and Niall, H. DNA 1, 155-162 (1982).

Hisaw, F.L. Proc. Soc. Exp. Biol. Med. 23 , 661-663 (1926).

Hudson, P., Haley, J., Cronk, M., Shine, J. and Niall, H. Nature, 291 , 127-131 (1981).

Hudson, P., Haley, J., John, M. Cronk, M., Crawford, R., Haralambidis, J., Tregear, G., Shine, J. and Niall, H. Structure of a genomic clone encoding biologically active human relaxin. Nature 301 , 628-631 (1983).

Huynh, T., Saint, R. and Davis, R. (1983) personal communication.

James, R., Niall, H., Kwok, S. and Bryant-Greenwood, G. Nature, 267 , 544-546 (1977).

John, M.J., Walsh, J.R., Borjesson, B.W. and Niall, H.D. Endocrinology 108 , 726-729 (1981).

Lawn, R.M., Fritsch, E.F., Parker, R.G., Blake, G. and Maniatis, T. all 15 , 1157-1174 (1978).

Maxam, A.M. and Gilbert, W. (1977) A new method for sequencing DNA. Proc. Natl. Acad. Sci. USA 74 , 560-564.
Morrison, D.A., In: Methods in Enzymology, R. Wu, ed. (New York : Academic Press) pp. 326-331 (1979).
Roychoudbury, R. Jay, E. and Wu, R. (1976) Terminal labelling and addition of homopolymer tracts to duplex DNA fragments by terminal deoxynucleotidyl transferase. Nucleic Acid Res. 3, 863-877 (1976).
Sanger, F., Coulson, A.R., Barrell, B.G., Smith, A.J.H. and Roe, B.A., J. Mol. Biol. 143 , 161-178 (1980).
Schwabe, C., Gowan, L.K. and Reinig, J.W., Ann. N.Y. Acad. Sci. 380 , 6-12 (1982).
Schwabe, C., McDonald, J.K. and Steinetz, B.C. Biochem. Biophys. Res. Commun. 75 , 503-510 (1977).
Southern, E.M., J. Mol. Biol. 98 , 503-517 (1975).
Taylor, J.M., Illmersee, R., and Summers, J.Biochim. Biophys. Acta 442 , 324-330 (1976).
Ullrich, A., Shine, J., Chirgwin, J., Picket, R., Tischer, E., Rutter, W.J. and Goodman, H.M. Rat insulin genes: construction of plasmids containing the coding sequences. Science 196 , 1313-1319 (1977).
Vogt, V.M. Purification and further properties of single-strand-specific nuclease from Aspergillus oryzae. Eur. J. Biochem. 33 , 192-200 (1973).
Wickers, M.P., Buell, G.N. and Schimke, R.T. Synthesis of double-stranded Dna complementary to lysozyme, ovomucoid, and ovalbumin mRNAs. J.Biol. Chem. 253, 2483-2495 (1978).

Claims

1. A DNA fragment encoding human H2-preprorelaxin, said H2-preprorelaxin having the amino acid sequence set out in Figure 2.

2. A DNA fragment encoding human H2-prorelaxin, said H2-prorelaxin having the amino acid sequence set out in Figure 2 with the exception that the signal sequence is excluded.

3. A DNA fragment encoding a polypeptide having human H2-relaxin activity, said polypeptide having an A-chain and a B-chain comprising the following amino acid sequences:

A-Chain

Gln Leu Tyr Ser Ala Leu Ala Asn Lys Cys Cys His Val Gly Cys Thr Lys Arg Ser Leu Ala Arg Phe Cys

B-Chain

Asp Ser Trp Met Glu Glu Val Ile Lys Leu Cys Gly Arg Glu Leu Val Arg Ala Gln Ile Ala Ile Cys Gly Met Ser Thr Trp Ser Lys Arg Ser Leu.

4. A DNA fragment encoding the signal A, B or C peptide chains of human H2-relaxin or any combination of two or more of said chains; wherein said peptide chains have the following amino acid sequences:

Signal Peptide

Met Pro Arg Leu Phe Phe Phe His Leu Leu Gly Val Cys Leu
Leu Leu Asn Gln Phe Ser Arg Ala Val Ala

A-Chain

Gln Leu Tyr Ser Ala Leu Ala Asn Lys Cys Cys His Val Gly
Cys Thr Lys Arg Ser Leu Ala Arg Phe Cys

B-Chain

Asp Ser Trp Met Glu Glu Val Ile Lys Leu Cys Gly Arg Glu
Leu Val Arg Ala Gln Ile Ala Ile Cys Gly Met Ser Thr Trp
Ser Lys Arg Ser Leu

C-Chain

Ser Gln Glu Asp Ala Pro Gln Thr Pro Arg Pro Val Ala Glu
Ile Val Pro Ser Phe Ile Asn Lys Asp Thr Glu Thr Ile Asn
Met Met Ser Glu Phe Val Ala Asn Leu Pro Gln Glu Leu Lys
Leu Thr Leu Ser Glu Met Gln Pro Ala Leu Pro Gln Leu Gln
Gln His Val Pro Val Leu Lys Asp Ser Ser Leu Leu Phe Glu
Glu Phe Lys Lys Leu Ile Arg Asn Arg Gln Ser Glu Ala Ala

Asp Ser Ser Pro Ser Glu Leu Lys Tyr Leu Gly Leu Asp Thr
His Ser Arg Lys Lys Arg.

5. A double-stranded DNA fragment encoding human H2-preprorelaxin, characterized in that it comprises a coding strand and a complementary strand corresponding to the following complete mRNA sequence:

AUG CCU CGC CUG UUU UUU UUC CAC CUG CUA GGA GUC UGU UUA
CUA CUG AAC CAA UUU UCC AGA GCA GUC GCG GAC UCA UGG AUG
GAG GAA GUU AUU AAA UUA UGC GGC CGC GAA UUA GUU CGC GCG
CAG AUU GCC AUU UGC GGC AUG AGC ACC UGG AGC AAA AGG UCU
CUG AGC CAG GAA GAU GCU CCU CAG ACA CCU AGA CCA GUG GCA
GAA AUU GUG CCA UCC UUC AUC AAC AAA GAU ACA GAA ACC AUA
AAU AUG AUG UCA GAA UUU GUU GCU AAU UUG CCA CAG GAG CUG
AAG UUA ACC CUG UCU GAG AUG CAG CCA GCA UUA CCA CAG CUA
CAA CAA CAU GUA CCU GUA UUA AAA GAU UCC AGU CUU CUC UUU
GAA GAA UUU AAG AAA CUU AUU CGC AAU AGA CAA AGU GAA GCC
GCA GAC AGC AGU CCU UCA GAA UUA AAA UAC UUA GGC UUG GAU
ACU CAU UCU CGA AAA AAG AGA CAA CUC UAC AGU GCA UUG GCU
AAU AAA UGU UGC CAU GUU GGU UGU ACC AAA AGA UCU CUU GCU
AGA UUU UGC UGA

6. A double-stranded DNA fragment encoding human H2-prorelaxin, characterized in that it comprises a coding strand and a complementary strand corresponding to the following mRNA sequence:

GAC UCA UGG AUG GAG GAA GUU AUU AAA UUA UGC GGC CGC GAA
UUA GUU CGC GCG CAG AUU GCC AUU UGC GGC AUG AGC ACC UGG
AGC AAA AGG UCU CUG AGC CAG GAA GAU GCU CCU CAG ACA CCU
AGA CCA GUG GCA GAA AUU GUG CCA UCC UUC AUC AAC AAA GAU
ACA GAA ACC AUA AAU AUG AUG UCA GAA UUU GUU GCU AAU UUG
CCA CAG GAG CUG AAG UUA ACC CUG UCU GAG AUG CAG CCA GCA
UUA CCA CAG CUA CAA CAA CAU GUA CCU GUA UUA AAA GAU UCC
AGU CUU CUC UUU GAA GAA UUU AAG AAA CUU AUU CGC AAU AGA
CAA AGU GAA GCC GCA GAC AGC AGU CCU UCA GAA UUA AAA UAC
UUA GGC UUG GAU ACU CAU UCU CGA AAA AAG AGA CAA CUC UAC
AGU GCA UUG GCU AAU AAA UGU UGC CAU GUU GGU UGU ACC AAA
AGA UCU CUU GCU AGA UUU UGC UGA

7. A double-stranded DNA fragment encoding the signal peptide, A, B or C peptide chains of human H2-preprorelaxin or a combination of any two or more of said chains characterized in that it comprises a coding strand and a complementary strand corresponding to the appropriate mRNA sequence or combination of the mRNA sequences given below:
Signal Peptide

AUG CCU CGC CUG UUU UUU UUC CAC CUG CUA GGA GUC UGU UUA
CUA CUG AAC CAA UUU UCC AGA GCA GUC GCG

A-Chain

CAA CUC UAC AGU GCA UUG GCU AAU AAA UGU UGC CAU GUU GGU
UGU ACC AAA AGA UCU CUU GCU AGA UUU UGC

B-Chain

GAC UCA UGG AUG GAG GAA GUU AUU AAA UUA UGC GGC CGC GAA
UUA GUU CGC GCG CAG AUU GCC AUU UGC GGC AUG AGC ACC UGG
AGC AAA AGG UCU CUG

C-Chain

AGC CAG GAA GAU GCU CCU CAG ACA CCU AGA CCA GUG GCA GAA
AUU GUG CCA UCC UUC AUC AAC AAA GAU ACA GAA ACC AUA AAU
AUG AUG UCA GAA UUU GUU GCU AAU UUG CCA CAG GAG CUG AAG
UUA ACC CUG UCU GAG AUG CAG CCA GCA UUA CCA CAG CUA CAA
CAA CAU GUA CCU GUA UUA AAA GAU UCC AGU CUU CUC UUU GAA
GAA UUU AAG AAA CUU AUU CGC AAU AGA CAA AGU GAA GCC GCA
GAC AGC AGU CCU UCA GAA UUA AAA UAC UUA GGC UUG GAU ACU
CAU UCU CGA AAA AAG AGA

8. A process for the production of a DNA fragment as set out in any one of claims 1 to 7, characterized in that it comprises screening a human cDNA clone bank using as a probe a fragment of human H1-relaxin DNA.

9. A process as claimed in claim 8, characterized in that the said fragment comprises nucleotides of C-peptide/A-peptide coding region of the human H1-relaxin DNA.

10. A DNA transfer vector, characterized in that it contains a cDNA deoxynucleotide sequences corresponding to a gene or DNA fragment as defined in any one of claims 1 to 7.

11. A DNA fragment, or DNA transfer vector as claimed in any one of claims 1 to 7 and 10, characterized in that one or more natural codons or their cDNA equivalents are replaced by another codon which codes for the same amino-acid.

12. A DNA transfer vector as claimed in claim 10 or 11, characterized in that it is a bacterial plasmid.

13. A DNA transfer vector as claimed in claims 10 or 11, characterized in that it is a bacteriophage DNA.

14. A cell transformed by a transfer vector as claimed in any one of claims 10 to 13.

15. A process for making a DNA transfer vector for use in maintaining and replicating a deoxynucleotide sequence coding for human H2-preprorelaxin or a sub-unit thereof according to any one of claims 1 to 7, characterized in that it comprises reacting said deoxynucleotide sequence with a DNA molecule prepared by cleaving a transfer vector with a restriction enzyme.

16. A process for making a fusion protein comprising an amino acid sequence consisting of all or part of the amino acid sequence of human H2-prorelaxin as its C-terminal sequence and a protein of a prokaryotic protein as its N-terminal sequence, characterised in that it comprises incubating a microorganism transformed by an expression transfer vector comprising the appropriate deoxynucleotide sequence.

17. A process for synthesizing human H2-prorelaxin comprising the A and B peptides separated from each other by a C peptide, characterized in that it comprises incubating a microorganism, transformed by an expression transfer vector comprising a deoxynucleotide sequence coding for said human prorelaxin under conditions suitable for expression of said sequence coding for human prorelaxin, and purifying human prorelaxin from the lysate or culture medium of said microorganism.

18. A fusion protein comprising an amino acid sequence characterized in that it consists of all or part of the amino acid sequence of human H2-prorelaxin as its C-terminal sequence and a portion of a prokaryotic protein as its N-terminal sequence.

19. Synthetic human H2-preprorelaxin having the amino acid sequence as set out in Figure 2.

20. Synthetic human H2-prorelaxin having the amino sequence as set out in figure 2 with the exception that the signal sequence is excluded.

21. A polypeptide having human H2-relaxin activity, said polypeptide having a disulphide bonded A-chain and B-chain comprising the following amino acid sequences:

A-Chain

Gln Leu Tyr Ser Ala Leu Ala Asn Lys Cys Cys His Val Gly
Cys Thr Lys Arg Ser Leu Ala Arg Phe Cys

B-Chain

Asp Ser Trp Met Glu Glu Val Ile Lys Leu Cys Gly Arg Glu
Leu Val Arg Ala Gln Ile Ala Ile Cys Gly Met Ser Thr Trp
Ser Lys Arg Ser Leu.

Revendications

1. Fragment d'ADN codant pour la préprorelaxine H2 humaine, ladite préprorelaxine H2 comportant la séquence d'aminoacides représentée sur la figure 2.

2. Fragment d'ADN codant pour la prorelaxine H2 humaine, ladite prorelaxine H2 comportant la séquence d'aminoacides représentée sur la figure 2, mis à part que la séquence signal est exclue.

3. Fragment d'ADN codant pour un polypeptide ayant une activité de relaxine H2 humaine, ledit polypeptide comportant une chaîne A et une chaîne B comprenant les séquences d'aminoacides suivantes:

Chaîne A

Gln Leu Tyr Ser Ala Leu Ala Asn Lys Cys Cys His Val Gly Cys Thr Lys Arg Ser Leu Ala Arg Phe Cys

Chaîne B

Asp Ser Trp Met Glu Glu Val Ile Lys Leu Cys Gly Arg Glu Leu Val Arg Ala Gln Ile Ala Ile Cys Gly Met Ser Thr Trp Ser Lys Arg Ser Leu.

4. Fragment d'ADN codant pour les chaînes de peptides signal, A, B ou C de la relaxine H2 humaine ou pour une combinaison quelconque de deux desdites chaînes ou plus; lesdites chaînes peptidiques comportant les séquences d'aminoacides suivantes:

Peptide signal

Met Pro Arg Leu Phe Phe Phe His Leu Leu Gly Val Cys Leu Leu Leu Asn Gln Phe Ser Arg Ala Val Ala

Chaîne A

Gln Leu Tyr Ser Ala Leu Ala Asn Lys Cys Cys His Val Gly Cys Thr Lys Arg Ser Leu Ala Arg Phe Cys

Chaîne B

Asp Ser Trp Met Glu Glu Val Ile Lys Leu Cys Gly Arg Glu Leu Val Arg Ala Gln Ile Ala Ile Cys Gly Met Ser Thr Trp Ser Lys Arg Ser Leu

Chaîne C

Ser Gln Glu Asp Ala Pro Gln Thr Pro Arg Pro Val Ala Glu Ile Val Pro Ser Phe Ile Asn Lys Asp Thr Glu Thr Ile Asn Met Met Ser Glu Phe Val Ala Asn Leu Pro Gln Glu Leu Lys Leu Thr Leu Ser Glu Met Gln Pro Ala Leu Pro Gln Leu Gln Gln His Val Pro Val Leu Lys Asp Ser Ser Leu Leu Phe Glu Glu Phe Lys Lys Leu Ile Arg Asn Arg Gln Ser Glu Ala Ala Asp Ser Ser Pro Ser Glu Leu Lys Tyr Leu Gly Leu Asp Thr His Ser Arg Lys Lys Arg.

5. Fragment d'ADN bicaténaire codant pour la préprorelaxine H2 humaine, caractérisé en ce qu'il comprend un brin codant et un brin complémentaire correspondant à la séquence d'ARNm complète suivante:

AUG CCU CGC CUG UUU UUU UUC CAC CUG CUA GGA GUC UGU UUA
CUA CUG AAC CAA UUU UCC AGA GCA GUC GCG GAC UCA UGG AUG
GAG GAA GUU AUU AAA UUA UGC GGC CGC GAA UUA GUU CGC GCG
CAG AUU GCC AUU UGC GGC AUG AGC ACC UGG AGC AAA AGG UCU
CUG AGC CAG GAA GAU GCU CCU CAG ACA CCU AGA CCA GUG GCA
GAA AUU GU CCA UCC UUC AUC AAC AAA GAU ACA GAA ACC AUA
AAU AUG AUG UCA GAA UUU GUU GCU AAU UUG CCA CAG GAG CUG
AAG UUA ACC CUG UCU GAG AUG CAG CCA GCA UUA CCA CAG CUA
CAA CAA CAU GUA CCU GUA UUA AAA GAU UCC AGU CUU CUC UUU
GAA GAA UUU AAG AAA CUU AUU CGC AAU AGA CAA AGU GAA GCC
GCA GAC AGC AGU CCU UCA GAA UUA AAA UAC UUA GGC UUG GAU
ACU CAU UCU CGA AAA AAG AGA CAA CUC UAC AGU GCA UUG GCU
AAU AAA UGU UGC CAU GUU GGU UGU ACC AAA AGA UCU CUU GCU
AGA UUU UGC UGA

6. Fragment d'ADN bicaténaire codant pour la prorelaxine H2 humaine, caractérisé en ce qu'il comprend un brin codant et un brin complémentaire correspondant à la séquence d'ARNm suivante:

GAC UCA UGG AUG CAG GAA GUU AUU AAA UUA UGC GGC CGC GAA
UUA GUU CGC GCG CAG AUU GCC AUU UGC GGC AUG AGC ACC UGG
AGC AAA AGG UCU CUG AGC CAG GAA GAU GCU CCU CAG ACA CCU
AGA CCA GUG GCA GAA AUU GUG CCA UCC UUC AUC AAC AAA GAU
ACA GAA ACC AUA AAU AUG AUG UCA GAA UUU GUU GCU AAU UUG
CCA CAG GAG CUG AAG UUA ACC CUG UCU GAG AUG CAG CCA GCA
UUA CCA CAG CUA CAA CAA CAU GUA CCU GUA UUA AAA GAU UCC
AGU CUU CUC UUU GAA GAA UUU AAG AAA CUU AUU CGC AAU AGA
CAA AGU GAA GCC GCA GAC AGC AGU CCU UCA GAA UUA AAA UAC
UUA GGC UUG GAU ACU CAU UCU CGA AAA AAG AGA CAA CUC UAC
AGU GCA UUG GCU AAU AAA UGU UGC CAU GUU GGU UGU ACC AAA
AGA UCU CUU GCU AGA UUU UGC UGA

7. Fragment d'ADN bicaténaire codant pour le peptide signal, les chaînes peptidiques A, B ou C de la préprorelaxine H2 humaine ou pour une combinaison de deux quelconques desdites chaînes ou plus, caractérisé en ce qu'il comprend un brin codant et un brin complémentaire correspondant à la séquence d'ARNm appropriée ou à une combinaison des séquences d'ARNm données ci-dessous:

Peptide signal

AUG CCU CGC CUG UUU UUU UUC CAC CUG CUA GGA GUC UGU UUA
CUA CUG AAC CAA UUU UCC AGA GCA GUC GCG

Chaîne A

CAA CUC UAC AGU GCA UUG GCU AAU AAA UGU UGC CAU GUU GGU
UGU ACC AAA AGA UCU CUU GCU AGA UUU UGC

Chaîne B

GAC UCA UGG AUG GAG GAA GUU AUU AAA UUA UGC GGC CGC GAA
UUA GUU CGC GCG CAG AUU GCC AUU UGC GGC AUG AGC ACC UGG
AGC AAA AGG UCU CUG

Chaîne C

AGC CAG GAA GAU GCU CCU CAG ACA CCU AGA CCA GUG GCA GAA
AUU GUG CCA UCC UUC AUC AAC AAA GAU ACA GAA ACC AUA AAU
AUG AUG UCA GAA UUU GUU GCU AAU UUG CCA CAG GAG CUG AAG
UUA ACC CUG UCU GAG AUG CAG CCA GCA UUA CCA CAG CUA CAA
CAA CAU GUA CCU GUA UUA AAA GAU UCC AGU CUU CUC UUU GAA
GAA UUU AAG AAA CUU AUU CGC AAU AGA CAA AGU GAA GCC GCA
GAC AGC AGU CCU UCA GAA UUA AAA UAC UUA GGC UUG GAU ACU
CAU UCU CGA AAA AAG AGA

8. Procédé pour la production d'un fragment d'ADN selon l'une quelconque des revendications 1 à 7, caractérisé en ce qu'il comprend le criblage d'une banque de clones d'ADNc humains avec utilisation en tant que sonde d'un fragment d'ADN de relaxine H1 humaine.

9. Procédé selon la revendication 8, caractérisé en ce que ledit fragment comprend des nucléotides de la région codant pour le peptide C/peptide A de l'ADN de la relaxine H1 humaine.

10. Vecteur de transfert d'ADN, caractérisé en ce qu'il contient une séquence de désoxynucléotides d'ADNc correspondant à un gène ou fragment d'ADN tel que défini dans l'une quelconque des revendications 1 à 7.

11. Fragment d'ADN ou vecteur de transfert d'ADN selon l'une quelconque des revendications 1 à 7 et 10, caractérisé en ce qu'un ou plusieurs codons naturels ou leurs équivalents d'ADNc sont remplacés par un autre codon qui code pour le même aminoacide.

12. Vecteur de transfert d'ADN selon la revendication 10 ou 11, caractérisé en ce qu'il est un plasmide bactérien.

13. Vecteur de transfert d'ADN selon la revendication 10 ou 11, caractérisé en ce qu'il est un ADN de bactériophage.

14. Cellule transformée par un vecteur de transfert selon l'une quelconque des revendications 10 à 13.

15. Procédé pour la production d'un vecteur de transfert d'ADN pour utilisation dans le maintien et la

réplication d'une séquence de désoxynucléotides codant pour la préprorelaxine H2 humaine ou une sous-unité de celle-ci selon l'une quelconque des revendications 1 à 7, caractérisé en ce qu'il comprend la mise en réaction d'une telle séquence de désoxynucléotides avec une molécule d'ADN obtenue par coupure d'un vecteur de transfert par une enzyme de restriction.

16. Procédé pour la production d'une protéine fusionnée comprenant une séquence d'aminoacides constituée de l'ensemble ou d'une partie de la séquence d'aminoacides de la prorelaxine H2 humaine en tant que sa séquence C-terminale, et une portion de protéine de procaryote en tant que sa séquence N-terminale, caractérisé en ce qu'il comprend l'incubation d'un micro-organisme transformé par un vecteur de transfert d'expression comprenant la séquence de désoxynucléotides appropriée.

17. Procédé pour la synthèse de prorelaxine H2 humaine comprenant les peptides A et B séparés l'un de l'autre par un peptide C, caractérisé en ce qu'il comprend l'incubation d'un micro-organisme transformé par un vecteur de transfert d'expression comprenant une séquence de désoxynucléotides codant pour ladite prorelaxine humaine, dans des conditions appropriées à l'expression de ladite séquence codant pour la prorelaxine humaine, et la purification de la prorelaxine humaine à partir du lysat ou du milieu de culture dudit micro-organisme.

18. Protéine fusionnée comportant une séquence d'aminoacides, caractérisée en ce qu'elle consiste en l'ensemble ou une partie de la séquence d'aminoacides de la prorelaxine H2 humaine en tant que sa séquence C-terminale, et une portion d'une protéine de procaryote en tant que sa séquence N-terminale.

19. Préprorelaxine H2 humaine de synthèse, comportant la séquence d'aminoacides telle que représentée sur la figure 2.

20. Prorelaxine H2 humaine de synthèse, comportant la séquence d'aminoacides telle que représentée sur la figure 2, mis à part que la séquence signal est exclue.

21. Polypeptide ayant une activité de relaxine H2 humaine, ledit polypeptide comportant une chaîne A et une chaîne B liées par pont disulfure, comprenant les séquences d'aminoacides suivantes:

Chaîne A

Gln Leu Tyr Ser Ala Leu Ala Asn Lys Cys Cys His Val Gly Cys Thr Lys Arg Ser Leu Ala Arg Phe Cys

Chaîne B

Asp Ser Trp Met Glu Glu Val Ile Lys Leu Cys Gly Arg Glu Leu Val Arg Ala Gln Ile Ala Ile Cys Gly Met Ser Thr Trp Ser Lys Arg Ser Leu.

Ansprüche

1. Menschliches H2-Präprorelaxin kodierendes DNA-Fragment, wobei besagtes H2-Präprorelaxin die in Figur 2 dargestellte Aminosäuresequenz besitzt.

2. Menschliches H2-Prorelaxin kodierendes DNA-Fragment, wobei besagtes H2-Prorelaxin die in Figur 2 dargestellte Aminosäuresequenz besitzt, mit der Ausnahme, daß die Signalsequenz ausgeschlossen ist.

3. DNA-Fragment, das ein Polypeptid kodiert, welches die Aktivität von menschlichem H2-Relaxin besitzt, wobei besagtes Polypeptid eine A-Kette und eine B-Kette besitzt, welche die folgenden Aminosäuresequenzen umfassen:

A-Kette

Gln Leu Tyr Ser Ala Leu Ala Asn Lys Cys Cys His Val Gly
Cys Thr Lys Arg Ser Leu Ala Arg Phe Cys

B-Kette

Asp Ser Trp Met Glu Glu Val Ile Lys Leu Cys Gly Arg Glu
Leu Val Arg Ala Gln Ile Ala Ile Cys Gly Met Ser Thr Trp
Ser Lys Arg Ser Leu.

4. DNA-Fragment, das die Signal-, A-, B- oder C-Peptidketten von menschlichem H2-Relaxin oder irgendeine Kombination von zwei oder mehr besagter Ketten kodiert; wobei besagte Peptidketten die folgenden Aminosäuresequenzen besitzen:

Signal-Peptid

Met Pro Arg Leu Phe Phe Phe His Leu Leu Gly Val Cys Leu
Leu Leu Asn Gln Phe Ser Arg Ala Val Ala

A-Kette

Gln Leu Tyr Ser Ala leu Ala Asn Lys Cys Cys His Val Gly
Cys Thr Lys Arg Ser Leu Ala Arg Phe Cys

B-Kette

Asp Ser Trp Met Glu Glu Val Ile Lys Leu Cys Gly Arg Glu
Leu Val Arg Ala Gln Ile Ala Ile Cys Gly Met Ser Thr Trp
Ser Lys Arg Ser Leu

C-Kette

Ser Gln Glu Asp Ala Pro Gln Thr Pro Arg Pro Val Ala Glu
Ile Val Pro Ser Phe Ile Asn Lys Asp Thr Glu Thr Ile Asn
Met Met Ser Glu Phe Val Ala Asn Leu Pro Gln Glu Leu Lys
Leu Thr Leu Ser Glu Met Gln Pro Ala Leu Pro Gln Leu Gln
Gln His Val Pro Val Leu Lys Asp Ser Ser Leu Leu Phe Glu
Glu Phe Lys Lys Leu Ile Arg Asn Arg Gln Ser Glu Ala Ala
Asp Ser Ser Pro Ser Glu Leu Tyr Leu Gly Leu Asp Thr His
Ser Arg lys Lys Arg.

5. Doppelsträngiges, menschliches H2-Präprorelaxin kodierendes DNA-Fragment, dadurch gekennzeichnet, daß es einen kodierenden Strang und einen komplementären Strang entsprechend der folgenden vollständigen mRNA-Sequenz umfaßt:

AUG CCU CGC CUG UUU UUU UUC CAC CUG CUA GGA GUC UGU UUA
CUA CUG AAC CAA UUU UCC AGA GCA GUC GCG GAC UCA UGG AUG
GAG GAA GUU AUU AAA UUA UGC GGC CGC GAA UUA GUU CGC GCG
CAG AUU GCC AUU UGC GGC AUG AGC ACC UGG AGC AAA AGG UCU

CUG AGC CAG GAA GAU GCU CCU CAG ACA CCU AGA CCA GUG GCA
GAA AUU GUG CCA UCC UUC AUC AAC AAA GAU ACA GAA ACC AUA
AAU AUG AUG UCA GAA UUU GUU GCU AAU UUG CCA CAG GAG CUG
AAG UUA ACC CUG UCU GAG AUG CAG CCA GCA UUA CCA CAG CUA
CAA CAA CAU GUA CCU GUA UUA AAA GAU UCC AGU CUU CUC UUU
GAA GAA UUU AAG AAA CUU AUU CGC AAU AGA CAA AGU GAA GCC
GCA GAC AGC AGU CCU UCA GAA UUA AAA UAC UUA GGC UUG GAU
ACU CAU UCU CGA AAA AAG AGA CAA CUC UAC AGU GCA UUG GCU
AAU AAA UGU UGC CAU GUU GGU UGU ACC AAA AGA UCU CUU GCU
AGA UUU UGC UGA

6. Doppelsträngiges, menschliches H2-Prorelaxin kodierendes DNA-Fragment, dadurch gekennzeichnet, daß es einen kodierenden Strang und einen komplementären Strang entsprechend der folgenden mRNA-Sequenz umfaßt:

GAC UCA UGG AUG GAG GAA GUU AUU AAA UUA UGC GGC CGC GAA
UUA GUU CGC GCG CAG AUU GCC AUU UGC GGC AUG AGC ACC UGG
AGC AAA AGG UCU CUG AGC CAG GAA GAU GCU CCU CAG ACA CCU
AGA CCA GUG GCA GAA AUU GUG CCA UCC UUC AUC AAC AAA GAU
ACA GAA ACC AUA AAU AUG AUG UCA GAA UUU GUU GCU AAU UUG
CCA CAG GAG CUG AAG UUA ACC CUG UCU GAG AUG CAG CCA GCA
UUA CCA CAG CUA CAA CAA CAU GUA CCU GUA UUA AAA GAU UCC
AGU CUU CUC UUU GAA GAA UUU AAG AAA CUU AUU CGC AAU AGA
CAA AGU GAA GCC GCA GAC AGC AGU CCU UCA GAA UUA AAA UAC
UUA GGC UUG GAU ACU CAU UCU CGA AAA AAG AGA CAA CUC UAC
AGU GCA UUG GCU AAU AAA UGU UGC CAU GUU GGU UGU ACC AAA
AGA UCU CUU GCU AGA UUU UGC UGA

7. Doppelsträngiges DNA-Fragment, das die Signalpeptid-, A-, B- oder C-Peptidketten von menschlichem H2-Präprorelaxin oder eine Kombination irgendwelcher zwei oder mehreren besagter Ketten kodiert, dadurch gekennzeichnet, daß es einen kodierenden Strang und einen komplementären Strang entsprechend der passenden mRNA-Sequenz oder der Kombination der unten angegebenen mRNA-Sequenzen umfaßt:

Signal-Peptid

AUG CCU CGC CUG UUU UUU UUC CAC CUG CUA GGA GUC UGU UUA
CUA CUG AAC CAA UUU UCC AGA GCA GUC GCG

A-Kette

CAA CUC UAC AGU GCA UUG GCU AAU AAA UGU UGC CAU GUU GGU
UGU ACC AAA AGA UCU CUU GCU AGA UUU UGC

B-Kette

GAC UCA UGG AUG GAG GAA GUU AUU AAA UUA UGC GGC CGC GAA
UUA GUU CGC GCG CAG AUU GCC AUU UGC GGC AUG AGC ACC UGG
AGC AAA AGG UCU CUG

C-Kette

AGC CAG GAA GAU GCU CCU CAG ACA CCU AGA CCA GUG GCA GAA
AUU GUG CCA UCC UUC AUC AAC AAA GAU ACA GAA ACC AUA AAU
AUG AUG UCA GAA UUU GUU GCU AAU UUG CCA CAG GAG CUG AAG
UUA ACC CUG UCU GAG AUG CAG CCA GCA UUA CCA CAG CUA CAA
CAA CAU GUA CCU GUA UUA AAA GAU UCC AGU CUU CUC UUU GAA
GAA UUU AAG AAA CUU AUU CGC AAU AGA CAA AGU GAA GCC GCA
GAC AGC AGU CCU UCA GAA UUA AAA UAC UUA GGC UUG GAU ACU
CAU UCU CGA AAA AAG AGA

8. Verfahren zur Herstellung eines DNA-Fragments nach einem der Ansprüche 1 bis 7, dadurch gekennzeichnet, daß es das Screenen einer menschlichen cDNA-Klonbank unter Verwendung eines Fragments von menschlicher H1-Relaxin-DNA als Sonde umfaßt.

9. Verfahren nach Anspruch 8, dadurch gekennzeichnet, daß das besagte Fragment Nukleotide der C-Peptid/A-Peptid-Kodierungsregion der menschlichen H1-Relaxin-DNA umfaßt.

10. DNA-Transfervektor, dadurch gekennzeichnet, daß er eine cDNA-Desoxynukleotidsequenz enthält, die einem Gen oder einem DNA-Fragment entspricht, wie es in einem der Ansprüche 1 bis 7 definiert ist.

11. DNA-Fragment oder DNA-Transfervektor nach einem der Ansprüche 1 bis 7 und 10, dadurch gekennzeichnet, daß eines oder mehrere natürliche Codons oder ihre cDNA-Äquivalente durch einen anderen Codon ersetzt sind, der für dieselbe Aminosäure kodiert.

12. DNA-Transfervektor nach Anspruch 10 oder 11, dadurch gekennzeichnet, daß er ein bakterielles Plasmid ist.

13. DNA-Transfervektor nach Anspruch 10 oder 11, dadurch gekennzeichnet, daß er eine Bakteriophagen-DNA ist.

14. Zelle, transformiert von einem Transfervektor nach einem der Ansprüche 10 bis 13.

15. Verfahren zum Herstellen eines DNA-Transfervektors zur Verwendung bei der Erhaltung und Replikation einer Desoxynukleotidsequenz, die für menschliches H2-Präprorelaxin oder eine Untereinheit desselben nach einem der Ansprüche 1 bis 7 kodiert, dadurch gekennzeichnet, daß es das Umsetzen besagter Desoxynukleotidsequenz mit einem DNA-Molekül umfaßt, das durch Schneiden eines Transfervektors mit einem Restriktionsenzym hergestellt ist.

16. Verfahren zum Herstellen eines Fusionsproteins, das eine Aminosäuresequenz umfaßt, die in ihrer Gesamtheit oder zum Teil aus der Aminosäuresequenz von menschlichen H2-Prorelaxin als ihrer C-terminalen Sequenz und einem Teil eines prokaryontischen Proteins als ihrer N-terminalen Sequenz besteht, dadurch gekennzeichnet, daß es das Inkubieren eines Mikroorganismus umfaßt, der von einem Expressions-Transfervektor transformiert ist, welcher die passende Desoxynukleotidsequenz umfaßt.

17. Verfahren zum Synthetisieren von menschlichem H2-Prorelaxin, das die A- und B-Peptide, von einem C-Peptid voneinander getrennt, umfaßt, dadurch gekennzeichnet, daß es das Inkubieren eines Mikroorganismus, der von einem Expressions-Transfervektor transformiert ist, welcher eine Desoxynukleotidsequenz umfaßt, die für besagtes menschliches Prorelaxin kodiert, unter für die Expression besagter für menschliches Prorelaxin kodierenden Sequenz geeigneten Bedingungen, und das Reinigen menschlichen Prorelaxins aus dem Lysat oder Kulturmedium von besagtem Mikroorganismus umfaßt.

18. Fusionsprotein mit einer Aminosäuresequenz, dadurch gekennzeichnet, daß sie in ihrer Gesamtheit oder zum Teil aus der Aminosäuresequenz von menschlichem H2-Prorelaxin als ihrer C-terminalen Sequenz mit einem Teil eines prokaryontischen Proteins als ihrer N-terminalen Sequenz besteht.

19. Synthetisches menschliches H2-Präprorelaxin mit der in Figur 2 dargestellten Aminosäuresequenz.

20. Synthetisches menschliches H2-Prorelaxin mit der in Figur 2 dargestellten Aminosäuresequenz, mit der Ausnahme, daß die Signal-Sequenz ausgeschlossen ist.

21. Polypeptid mit der Aktivität von menschlichem H2-Relaxin, wobei besagtes Polypeptid eine disulfidgebundene A-Kette und B-Kette aufweist, welche die folgenden Aminosäuresequenzen umfassen:

A-Kette

Gln Leu Tyr Ser Ala Leu Ala Asn Lys Cys Cys His Val Gly
Cys Thr Lys Arg Ser Leu Ala Arg Phe Cys

B-Kette

Asp Ser Trp Met Glu Glu Val Ile Lys Leu Cys Gly Arg Glu
Leu Val Arg Ala Gln Ile Ala Ile Cys Gly Met Ser Thr Trp
Ser Lys Arg Ser Leu.

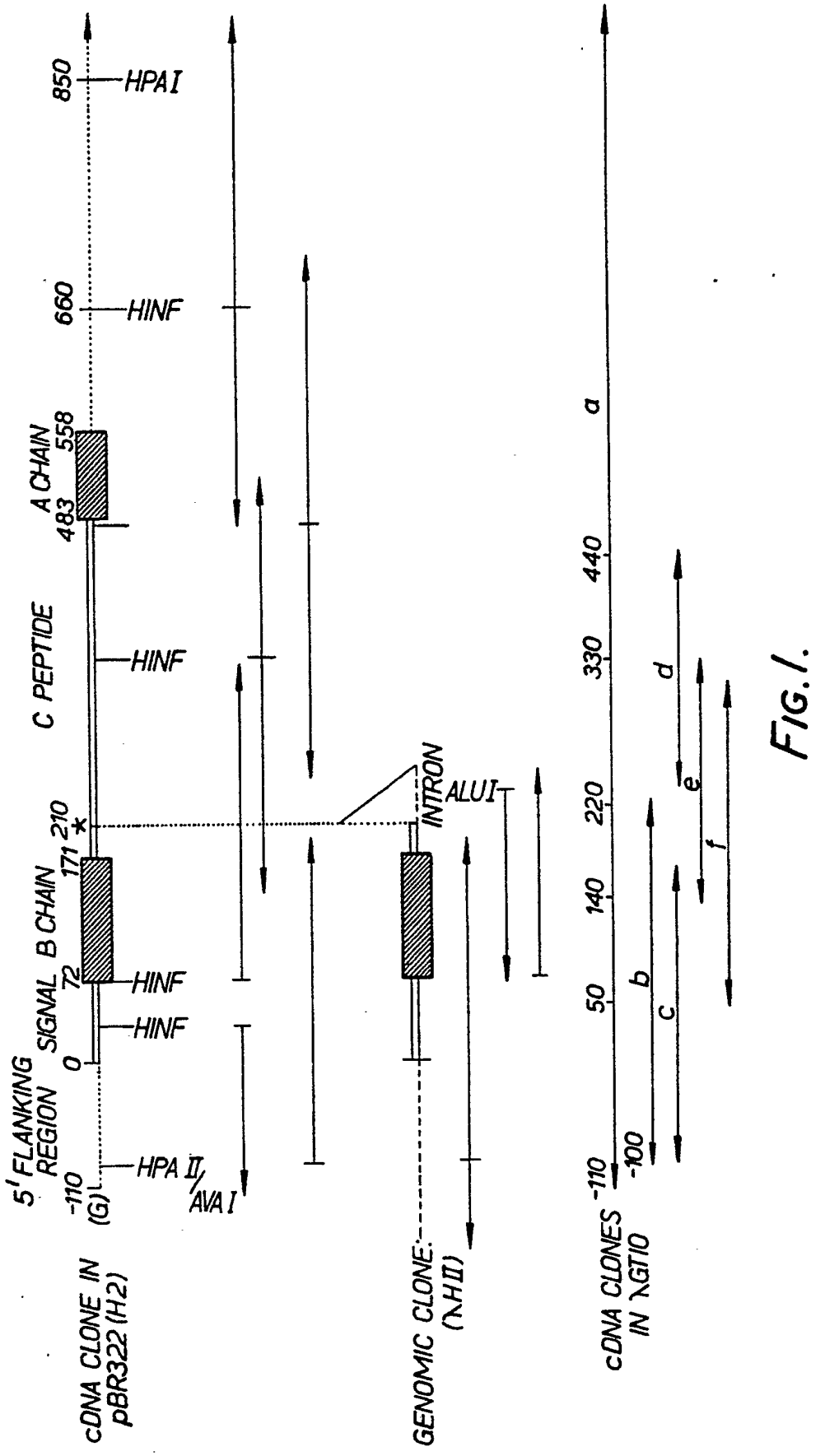

850
HPA I
660
HINF
A CHAIN
558
483
C PEPTIDE
HINF
210
171
INTRON
ALU I
SIGNAL B CHAIN
72
HINF
HINF
0
5' FLANKING REGION
-110
(G)
HPA II/ AVA I
cDNA CLONE IN pBR322 (H2)
GENOMIC CLONE (λH II)
a
440
330
d
220
e
f
140
50
b
c
-100
-110
cDNA CLONES IN λGT10

FIG. 1.

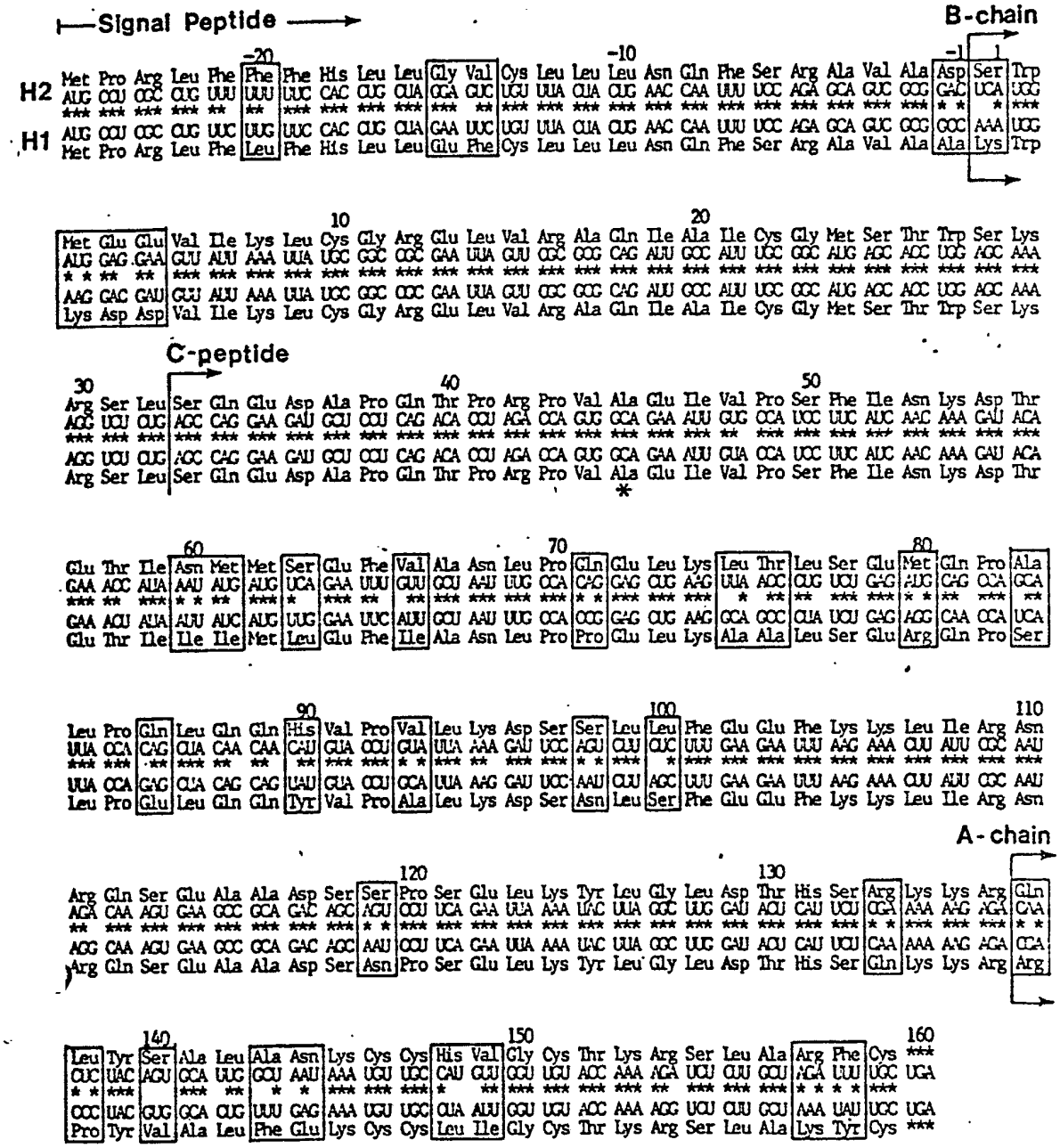


FIGURE 2.

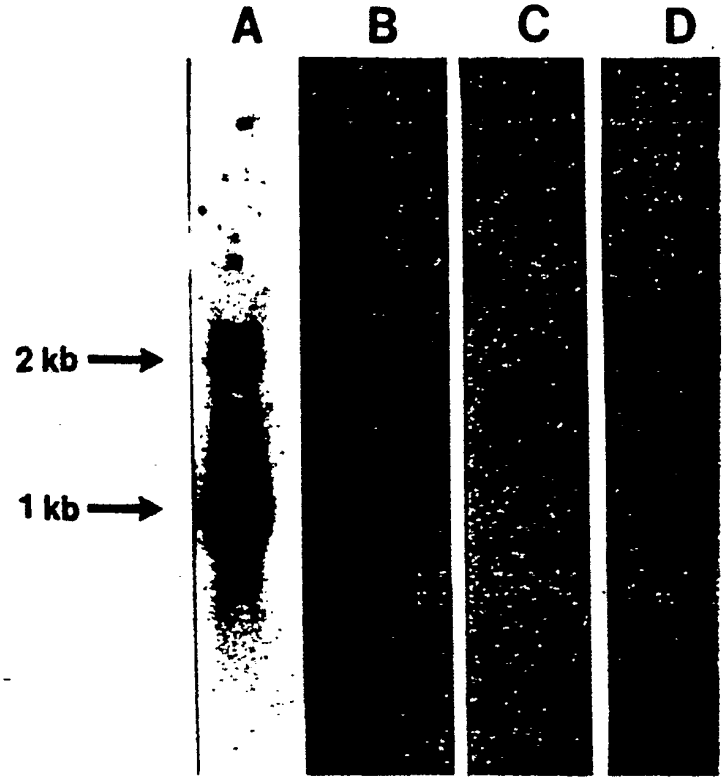


FIG. 3a.

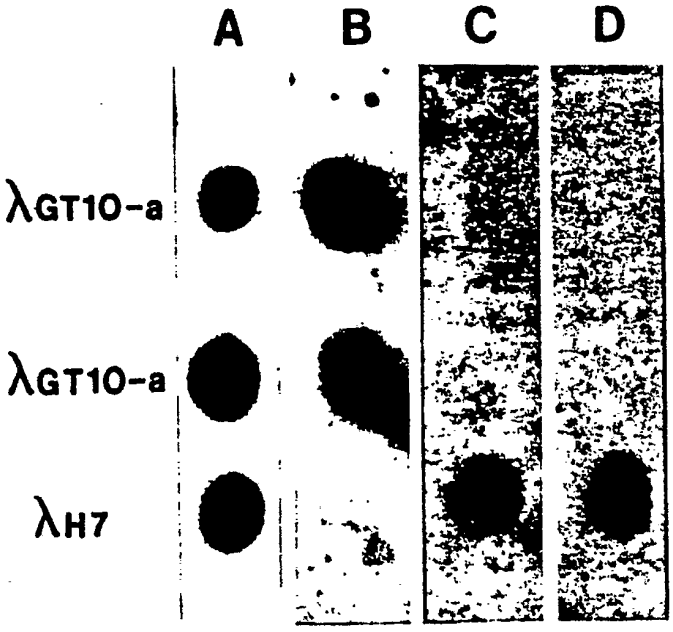


FIG. 3b.

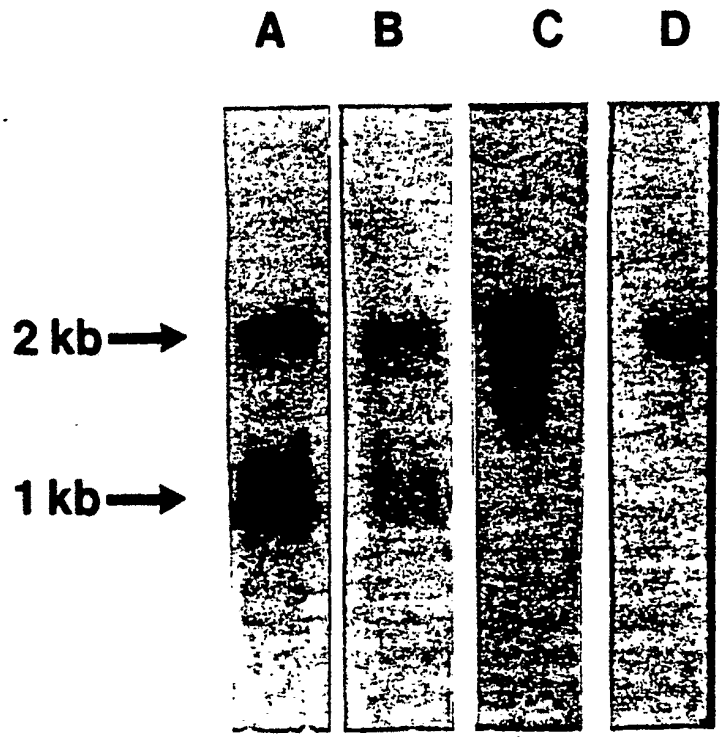


FIG. 4.

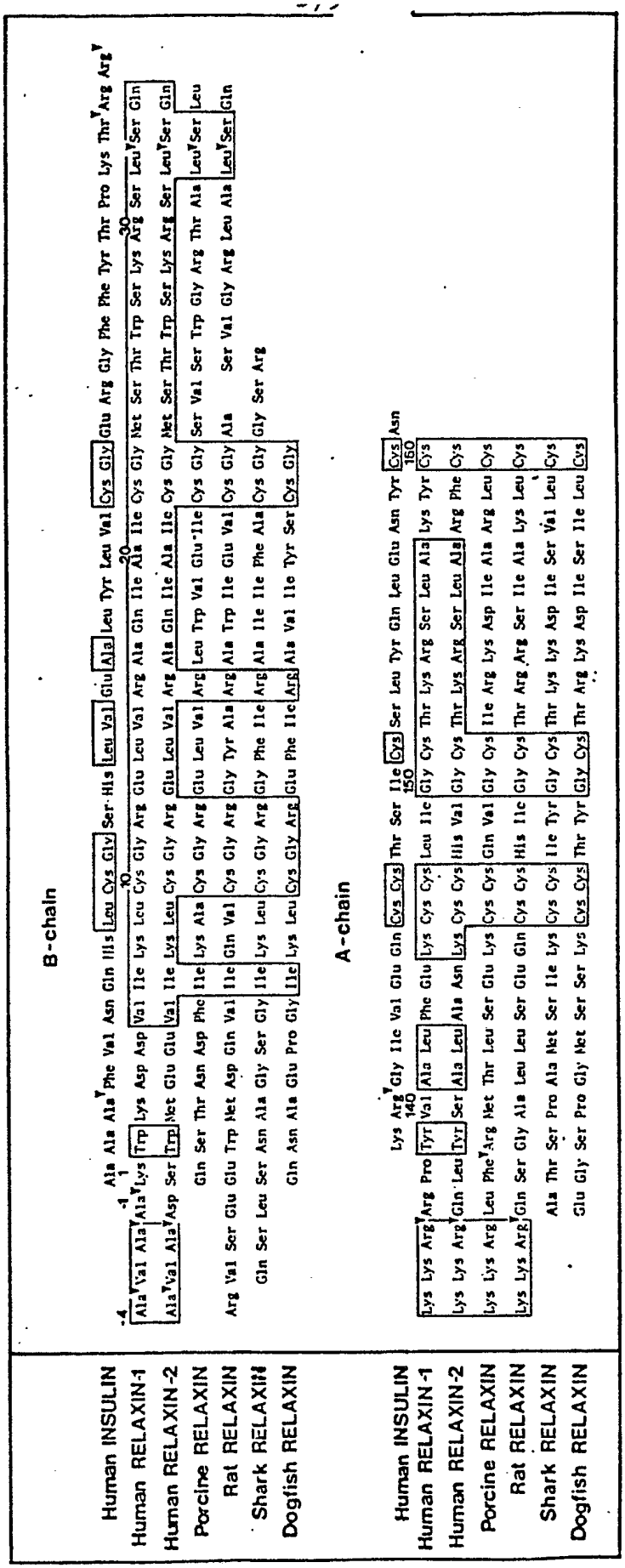

B-chain
A-chain
Human INSULIN
Human RELAXIN-1
Human RELAXIN-2
Porcine RELAXIN
Rat RELAXIN
Shark RELAXIN
Dogfish RELAXIN

FIGURE 5.

DOCUMENT 8

Translation of opposition of 9 January 1992 from Wilhelms Kilian & Partner to European Patent 0 112 149 (Application No: 83 307 553.4) in the name of HOWARD FLOREY INSTITUTE OF EXPERIMENTAL PHYSIOLOGY AND MEDICINE, Melbourne, Australia

---

On behalf of the Green Party in the European Parliament, namely the delegates M.-A. Aglietta, G. Amendola, J.-M. Bandres, V. Bettini, B. Boissiere, H. Breyer, R, Conan, B. Cramon-Daiber, N. van Dijk, M.-M. Dinguirard, B. Ernst de la Graete, E. Falqui, Y. Fremion, F.-W. Graefe zu Baringdorf, M.-A. Isler-Beguin, A. Langer, E. Melandri, G. Onesta, E.-M. Quistorp, J.-P. Raffin, C. Roth, P. Staes, M. Taradash, D. Tazdait, W. Telkämper, H. Verbeek, represented by the Party President Paul Lannoye, European Parliament, 93, rue Belliard, B-1047 Brussels, Belgium, opposition is hereby filed against the above European patent entitled "Molecular cloning and characterisation of a further gene sequence coding for human relaxin" in the name of HOWARD FLOREY INSTITUTE OF EXPERIMENTAL PHYSIOLOGY AND MEDICINE, University of Melbourne, Parkville Victoria, Australia.

We request that the patent be fully revoked. In the event of it not being possible to comply with the petition we request a hearing.

The opposition fee of DM 700 is being paid by the enclosed cheque.

The power of attorney will follow shortly.

Since a study of the relevant literature by the undersigned patent attorney and his telephone calls to the legal department of the European Patent Office did not indicate whether a Party of the European Parliament in the person of its President came under the heading of "anyone" having a legitimate interest in opposition under Article 99(1), Clause 1 of the EPC, this opposition is also being filed on behalf of Mr Paul Lannoye, President of the Green Party in the European Parliament. The above address applies for this Opponent as well. The opposition fee of DM 700 is being paid by the enclosed second cheque.

The power of attorney will follow shortly.

We file the above petitions.

Since both oppositions are identical, except for the actual opponents, we shall hereinafter use the term "opposition" instead of "oppositions".

The opposition is based on the fact that the subject matter of the European patent in suit is not patentable under Articles 52-57 EPC; more particularly the subject matter is not novel; nor is it based on inventive step, because it is obvious to the skilled man from the prior art; the subject matter does not involve an invention, but a discovery; furthermore, the publication or exploitation of the alleged invention infringes public order and morals.

The present opposition used the term "gene" although the claims refer to the gene as a "DNA fragment". In

actual fact, the applicants used the term "gene" consistently from 12 December 1983 to 23 March 1990. The term "DNA fragment" instead of "gene" was introduced by the European Patent Office in the communication under Rule 51(4) EPC.

I

According to the above patent, researchers looking for a first gene coding for human relaxin have now found a second gene which codes for human relaxin (lines 6 to 8, page 3 of the description).

This gene was isolated and purified from tissue previously taken from the ovary tissue of a pregnant woman.

The patent in suit was granted to this gene, parts of this gene, parts of the DNA containing this gene, polypeptides coded by this gene, parts of this gene, parts of the DNA containing this gene (and so on, see the claims).

The genes or DNA fragments according to claims 1 to 4 are given absolute protection.

On the other hand, they are described solely in respect of their ability to code. There is no reference whatsoever to their chemical composition, their chemical structure, their physical structure (secondary - tertiary structure), etc, similarly to the genes and DNA fragments according to claims 5 to 7, which are to

"comprise" the mRNA sequences indicated there but not "consist" of them.

Accordingly the patent protection at least of claims 1 to 4 covers genes or DNA fragments which are possibly contained in human genes but have not yet been discovered, and which in some cases are of a different or completely different composition from the genes according to the patent in suit. Accordingly, the genes or DNA fragments at least according to claims 1 to 4 are not patentable.

II

Obviously the gene is not novel; before its discovery, it was already contained in the tissue taken from the ovary of the pregnant woman.

In actual fact, it may be assumed that this gene in its basic composition and structure existed for tens of thousands of years in the ovary tissue of pregnant women and coded for human relaxin for an equal length of time.

The human gene cannot be invented by anyone because it was already "invented" long before man had the opportunity of discovering it.

"Isolating" and "purifying" the gene cannot form grounds for novelty even if this might appear to be formal grounds. As a DNA fragment the gene is present in man in a form which codes for human relaxin. The "degree of isolation" and "purity" in these conditions

is sufficient to satisfy the coding function. It may be assumed that the "isolated" and "purified" gene in accordance with the patent in suit has, in respect of its coding function, the same "degree of isolation" and "degree of purification" as in human DNA in man if, as required in the patent in suit, the identical relaxin is to be coded for.

It might be possible under the patent system to protect the "isolation" and "purification" of genes provided the other requirements such as novelty and inventive step exist for such processes, but this question can be left open because in the present case the "purification" and "isolation" are carried out in manner known per se.

The elucidation of the chemical structure has no patentability either, because it is effected in conventional manner known per se. Even if the structural analysis method were inventive, that might be patentable but this cannot form grounds for patentability of the gene per se.

It should also be noted that structural analyses are in some cases carried out by machine, so that in that respect it is not possible to refer to inventive step unless machines are to be granted inventor status in the future.

III

The general requirement for patenting a substance, which the applicant and the European Patent Office

obviously consider the human gene claimed to be, is that a method of its preparation should be fully disclosed.

The teaching in this respect in the patent in suit is as follows: "Take a woman who is pregnant, take tissue etc from her ovary..." (page 3, lines 40 to 46; page 10, lines 1 to 7 of the description).

In our view, an "invention" and hence the present "invention" at least offends against morals by exploiting the extreme condition of a woman, pregnancy, removing tissue from her ovary, and using it as the basis of a profit-oriented technical process.

Breaking up the genes of humans in general and pregnant women in particular into DNA fragments or genes and transferring them into the private ownership of natural or legal personae under the monopoly of a patent to satisfy profit expectations will disgust anyone who considers that the inviolability of the dignity of man is an essential part of his humanity.

IV

The relevant statutory regulations for rejecting the patent in suit will be found in Article 53(a) EPC. The reference to this in the EPC Examination Directives to the effect that this provision will probably only be used in very rare and extreme cases, may be correct in the general area of patenting technical inventions, but the converse applies to the new field of genetic engineering developments.

We are convinced that this provision has been taken into account only superficially, if at all, in the present and in similar cases. This is all the more objectionable inasmuch as genetic engineering and its problems forms a new area which is developing at amazing speed in knowledge, results and risk, at a rate with which the discussion of the ethical components has in no way kept pace.

On the contrary, we are of the impression that the "rare" and "extreme" cases mentioned in the Examination Directives are the "normal" cases in most disclosed patent applications filed by the genetic industry, so that it is precisely in this area that the provision of Article 53(a) EPC acquires quite considerable significance.

The European Patent Office cannot argue that the questions of public morals and public order can be addressed subsequently at national level in possible revocation proceedings; Article 53(a) of the EPC, like the entire EPC, is a law common to the contractual states (Article 1 EPC).

The European Patent Office must therefore conscientiously observe this statutory regulation and the other patent granting requisites. In principle, if not, in our view, in quality, this has already been confirmed by the Appeals Senate in the "Krebsmaus" matter (EP 0 169 672).

In view of the peculiar nature of the association of the contracting states solely for the common law

governing the granting of patents of invention, the contracting states otherwise forming no unit whatsoever, and in the absence of any experience governing "public order" and "offence against public morals" in this association of states under the EPC, and in view of the significance of the basic question of the patenting of human genes and their copies, we request that the European Patent Office should make suitable enquiries in all contracting states or at least in those contracting states designated in the patent in suit, to clarify the question whether the publication or exploitation of the present invention does infringe against public order or public morals and whether patenting, i.e. the granting of a patent to human genes in accordance with the patent in suit by the European Patent Office, does or does not offend against infringe against public order or public morals.

It should be an easy matter for the European Patent Office to grant this petition, because the European Patent Office must be interested, in the interest of public order, in a basic clarification of the question of principle for communication to the public and for them to support; as an authority in a group of democratic states it should also counteract the impression of prematurely giving in to the pressure of a capital-intensive branch of industry without thoroughly, publicly and openly discussing or permitting the discussion of socially relevant questions, such as the ethics of patenting human genes or their copies, before any concluding decision is taken, and without any premature fait accompli.

From these aspects we cannot understand why this patent grant, like some others in this area, has not been postponed, despite the fact, for example, that the discussion of the directive of the EEC Commission regarding the legal protection of bio-engineering inventions has not been concluded, and the fact that a number of members of the commission of the EEC are contractual States of the EPC.

V

Since, in our view, human genes generally and the human gene according to the patent in suit, in particular, are not patentable, and nor are the processes for utilising the discovered gene or its discovered ability for coding for relaxin, etc, on an industrial scale, and since the processes claimed under the process claims are also known per se or obvious, as shown by the examination proceedings and the literature cited in the patent specification in the examination proceedings, the above petition for complete revocation of the patent is justified.

RELAXIN PATENT VALIDITY EXERCISE

ANNEX: DOCUMENT 9

EPO DECISION ON THE RELAXIN PATENT

EXTRACT FROM THE OFFICIAL JOURNAL OF THE EPO 6/1995 388

Note: It is suggested that this is studied after the validity exercise, for private study or to facilitate group discussion in the review of the exercise. This extract excludes material on procedural issues - where text has been omitted, this is indicated thus: […..]

Howard Florey/Relaxin

(Oppositions by Fraktion der Grünen im Europäischen Parlament; Lannoye)

HEADNOTE

Human H2-relaxin had no previously recognised existence. The patentee had developed a process for obtaining H2-relaxin and the DNA encoding it, had characterised these products by their chemical structure and had found a use of the protein. Typical claims (set out in full in the Annex to the Decision) of the granted patent were:

1. A DNA fragment encoding human H2-preprorelaxin, said H2- preprorelaxin having the amino acid sequence set out in Figure 2.

2. A DNA fragment encoding human H2-prorelaxin, said H2-prorelaxin having the amino acid sequence set out in Figure 2 with the exception that the signal sequence is excluded.

3. A DNA fragment encoding a polypeptide having human H2-relaxin activity, said polypeptide having an A-chain and a B-chain comprising the following amino acid sequences:

[see earlier copy of full patent document- Document 7 in this Annex]

[….]

19. Synthetic human H2-preprorelaxin having the amino acid sequence as set out in Figure 2.

20. Synthetic human H2-prorelaxin having the amino sequence as set out in Figure 2 with the exception that the signal sequence is excluded.

21. A polypeptide having human H2-relaxin activity, said polypeptide having a disulphide bonded A-chain and B-chain comprising the following amino acid sequences:

[see earlier copy of full patent document]

Opposition had been entered by the Fraktion der Grünen, and separately by their Fraktionspräsident (Paul Lannoye), under Articles 100(a) and (b). However, no prior art was cited in respect of the lack of inventive step, the closest state of the art for the subject-matter of Claim 1 being, according to the opponents, the woman from whom the mRNA used to prepare the H2-relaxin cDNA was isolated.

Three days before the oral proceedings the patentee submitted a declaration by Professor E.A. Bauer. The patentee also questioned the admissibility of the opposition by opponent 01, but without specifically requesting that it be declared inadmissible. The issue of admissibility of an opposition filed in the name of a political fraction had also been canvassed in earlier telephone discussions between the formalities officer and the opponents.

Held, by the Opposition Division, rejecting the oppositions:

[…..]

4. Since it was common ground among the parties that, until a cDNA encoding H2-relaxin and its precursors had been isolated by the patentee, the existence of this form of relaxin was unknown, the novelty of the granted claims was assured.

5. The opponents' argument as to lack of inventive step failed for the reason that the gene was novel. In isolating the DNA encoding human H2- relaxin the patentee was therefore not preparing a known substance by conventional means but instead providing to the public for the first time a product whose existence was previously unknown.

6. The opponents' argument that the subject-matter of the patent represented a mere discovery was wrong. The consequences asserted by the opponents as to the patentability of such discoveries as the moon (after the Americans landed on it in 1969), *Otzi* (a mummified, around 5,000-year-old man found in the Italian-Austrian Alps) or a new animal found in some remote area, did not follow.

7. In relation to the objection under Article 53(a) (morality), the opponents' arguments as to slavery and the dismemberment of women betrayed a fundamental misunderstanding of the effects of a patent.
8. The argument that human life was being patented was also unfounded, DNA not being 'life' but instead a chemical substance which carries genetic information and which can be used as an intermediate in the production of proteins which may be medically useful.

9. Pending the final formulation of the EU Directive on the legal protection of biotechnological inventions, it was inappropriate for the EPO to impose a moratorium on the patenting of human genes. Nor was there any legal mechanism in the EPC for doing so.

10. The opponents' request that the EPO carry out a referendum as to the public's view in Contracting States on what should be patented was misconceived. The burden of proof lay with the opponents. It was for them to carry out such survey, if they considered that it would assist their case.

11. The Article 53(a) exclusion on the grounds that an invention is contrary to morality was limited to the limited class of case where there was an overwhelming consensus that the exploitation or publication of an invention would be immoral.

[…..]

TEXT OF DECISION

Facts and Submissions

I. European patent No. 112 149 is based on European patent application No. 83307553.4 filed on 12December 1983 and claiming priority from AU 7247/82 filed on 13 December 1982. Mention of the grant of the patent was published in the European Patent Bulletin on 10 April 1991. The proprietor of the patent is the Howard Florey Institute of Experimental Physiology and Medicine.

II. Notice of Opposition was filed on 9 January 1992 by the Fraktion der Grünen im Europäischen Parlament (I) and separately, with an identical text, by their Fraktionspräsident, Mr Paul Lannoye (II).

II.1 The grounds for both oppositions were that the subject-matter of the patent is not patentable (Article100(a) EPC) for lack of novelty and inventive step (Articles 54 and 56 EPC respectively), that it represents a discovery and as such is not patentable under Article 52(2)(a) EPC, and that it offends against 'ordre public' or morality (Article 53(a) EPC). The opponents requested the revocation of the patent in its entirety. The only document cited was EP-A-169 672.

[……]

IV. Since all parties had requested oral proceedings, these were appointed with a communication dated 28 March 1994. In the annex to the summons, the preliminary opinion was further expressed that the subject-matter of the claims was novel and inventive and did not constitute a discovery. No comments on the objection under Article 53(a) EPC were made.

V. With letters dated 30 November 1994 and 2 December 1994, three third parties filed observations under Article 115(1) EPC expressing their opposition to the patenting of the present invention.

[……]

VIII. Oral proceedings took place on 8 December 1994. At oral proceedings the opponents submitted a request to have the Opposition Division declared partial, contending that partiality was demonstrated by an alleged gross mistake made in the annex to the summons to oral proceedings. This request was rejected after deliberation by the Opposition Division.

IX. At the end of the proceedings the chairman announced that the oppositions were rejected under Article102(2) EPC.

Reasons for the Decision

[…..]

3. Partiality

3.1 The opponents asserted that the preliminary opinion set out in the annex to the summons to oral proceedings contained a gross mistake and that this proved the Opposition Division to be biased in favour of the proprietor. This alleged mistake was the statement, made under point 3, lines 10 to 11, that the claimed [H2-relaxin] gene was in the form of a cDNA. According to the opponents, this was untrue since Claim 1 referred to a 'DNA', not a 'cDNA' fragment. The opponents also made much of the fact that the word 'gene', used in the claims of the application as filed, was changed to 'DNA fragment' on grant.

3.1.1 The committal of a gross error during opposition proceedings may indicate partiality but does not necessarily do so. However, no gross error has occurred. Claim 1 relates to a DNA fragment encoding human H2-preprorelaxin, said preprorelaxin having the amino acid sequence set out in Figure 2. This sequence is encoded by a cDNA derived from the H2-relaxin mRNA. The genomic DNA encodingH2-relaxin contains an intron interrupting the coding region (see page 11, lines 49 to 51, of the description). It is in consequence a fact that a DNA fragment encoding the amino acid sequence of Figure 2 (without the amino acids encoded by the intron) is not present in the human genome.

3.1.2 In the light of the above, the Opposition Division takes the view that Claim 1 is directed to a cDNA sequence encoding preprorelaxin despite the fact that the word 'cDNA' is not mentioned in the claim. The Division moreover wishes to emphasise that its decision in the present case would not be affected in anyway even if genomic DNA sequences encoding human relaxin were included in the scope of the claims. This issue is therefore irrelevant, as is the matter of the term 'DNA fragment' (introduced at the grant stage by the Examining Division for uniformity with the parallel human relaxin

patent EP-B-101 309) as opposed to 'gene'. These two terms will be used interchangeably throughout this decision.

3.2 The opponents further alleged that the preliminary conclusions set out in the above-mentioned annex acknowledging the novelty of the claims of the disputed patent and denying that the inventions constituted a discovery revealed partiality on the part of the Opposition Division since these issues had been decided without sufficiently hearing the parties. However, the Division cannot follow this argument either.

3.2.1 It is usual in opposition proceedings to send out together with the summons to oral proceedings a note in which the topics considered essential to discuss are identified and, if appropriate, provisional comments on the positions adopted by the parties are made (see Guidelines, C-VI, 3.2). In the present proceedings, the established practice of the European Patent Office with respect to the patentability of newly-isolated natural substances was considered to be so clear that it was felt to be justified to give an opinion on the issues of novelty and discovery in the annex to the summons to oral proceedings on the basis of the written submissions of the opponents. This did not mean that a final decision had been reached on these points, nor did it in any way preclude the opponents from presenting further arguments at oral proceedings. It should moreover be noted that no comment was made in the annex concerning the objection under Article 53(a)EPC.

3.3 In view of the above, the opponents' allegation of bias on the part of the Opposition Division is regarded as unfounded.

4. Novelty and inventive step (Articles 54 and 56 EPC)

4.1 The opponents contend that the subject-matter of the opposed patent lacks novelty since the gene encoding relaxin was always present in the female human body; the proprietor has merely isolated it in a conventional way. The Opposition Division does not agree.

4.2 First, as already explained above (see point 2.1 and onward), the claimed DNA fragments encoding relaxin and its precursors (prepro- and pro-forms) are cDNAs, that is, DNA copies of human mRNA encoding relaxin. cDNAs do not occur in the human body. The sequences of Claims 1 to 7 are hence novel for this reason alone.

4.3 Moreover, even if Claims 1 to 7 are interpreted as including in their scope genomic DNA fragments encoding H2-relaxin, there is no question of lack of novelty of these claims. According to Article 54(1)EPC, an invention shall be considered to be new if it does not form part of the state of the art. In Article54(2) EPC, the state of the art is defined as comprising everything *made available to the public* before the filing date of the European patent application (emphasis added).

4.3.1 It is common ground among the parties that until a cDNA encoding human H2-relaxin and its precursors was isolated by the proprietor, the existence of this form of relaxin was unknown. It is established patent practice to recognise novelty for a natural substance which has been isolated for the first time and which had no previously recognised existence (see Guidelines, C-IV, 2.3). Indeed, the opponents recognised that this principle may provide, in their words, a formal basis for novelty of the relaxin DNA(see Notices of Opposition, page 5, second sentence). In view of this practice, the novelty of the present claims is assured.

4.4 The opponents' assertion that Claims 1 to 4 are not patentable because the chemical structure of the DNA fragments of those claims is completely undefined cannot be accepted. The DNA is defined in terms of the amino acid sequence it encodes, a generally acceptable terminology and one which is widely used and perfectly understandable to the skilled person. It is true that a very large number of DNA sequences may fall under the scope of the claim, including sequences which possibly occur in nature and differ from those exemplified in the patent. However, this has no bearing on the patentability of the claims. It should be noted that alleged lack of clarity of claims or lack of support for their full scope are not grounds for opposition under Article 100 EPC.

4.5 In the light of the above, the claims are regarded as novel.

4.6 Lack of inventive step was also cited by the opponents as grounds for their opposition, on the basis of alleged lack of novelty of the claimed DNA fragments encoding H2-relaxin and the fact that the means used to isolate the DNA were conventional; according to the opponents, who cited no prior art, the closest state of the art for the subject-matter of Claim 1 is the woman from whom the mRNA used to prepare theH2-relaxin cDNA was isolated.

4.6.1 The opponents' argument must fail for the sole reason that the gene was not known, but is rather regarded as novel (see above). In isolating the DNA encoding human H2-relaxin, the proprietor was not preparing a known substance by conventional means, but providing to the public for the first time a product whose existence was previously unknown. This is regarded as inventive whatever the methods used to prepare the product. The claims are considered to involve an inventive step because there is no pertinent real prior art (as opposed to the ' woman') available rendering the claimed subject-matter obvious.

5. Discovery (Article 52(2) EPC)

5.1 The opponents further assert that the subject-matter of the patent represents a discovery and is hence not patentable under Article 52(2)(a) EPC. This argument ignores the long-standing practice of the European Patent Office concerning the patentability of natural substances. As explained in the *Guidelines*, C-IV, 2.3, to find a substance freely occurring in nature is mere discovery and therefore unpatentable. However, if a substance found in nature has first to be isolated from its surroundings and a process for obtaining it is developed, that process is patentable. Moreover, if this substance can be properly characterised by its structure and it is new in the absolute sense of having no previously recognised existence, then the substance *per se* may be patentable.

5.2 The above guideline is highly appropriate in the present case. Human H2- relaxin had no previously recognised existence. The proprietor has developed a process for obtaining H2-relaxin and the DNA encoding it, has characterised these products by their chemical structure and has found a use for the protein. The products are therefore patentable under Article 52(2) EPC.

5.3 The opponents complained that equating discoveries with inventions led to unduly broad patents which prevented anyone else from making, in the case at issue, a selection invention on H2-relaxin. However, the Opposition Division finds it perfectly justified to grant broad protection in view of the fact that H2-relaxin has been made available to the public for the first time. This does not exclude the possibility of further inventions, for example improved derivatives of the protein, better processes for its preparation, and so on. The situation is comparable to that existing for inventions relating to air pumps, to use the example repeatedly mentioned by the opponents, where the original inventor of an air pump would certainly have been entitled to a broad patent.

5.4 The opponents also contended that the above reasoning would mean that discoveries such as the moon (after the Americans landed on it in 1969), *Otzi* (a mummified, around 5,000-year-old man found in ice in the Italian-Austrian Alps) or a new animal found in some remote area would also be patentable. However, this is not the case. As already pointed out, the mere finding of something freely occurring in nature is not an invention. An invention must have a technical character, that is, should constitute an industrially applicable technical solution to a technical problem, and must be reproducibly obtainable without undue burden. A product must furthermore be novel in the sense of having had no previously recognised existence and must in addition be inventive. None of the discoveries cited by the opponents fulfil these criteria.

5.5 In conclusion, the subject-matter of the disputed patent does not represent a discovery and is hence not excluded from patentability under Article 52(2) EPC.

6. Morality (Article 53(a) EPC)

6.1 The opponents contended that the subject-matter of the disputed patent, insofar as it relates to a DNA fragment encoding human H2-relaxin and its precursors, offends against the provisions of Article 53(a). They argued essentially as follows:

> (a) The patent teaches that in order to repeat the invention, tissue is to be taken from a pregnant woman. The isolation of the DNA relaxin gene from tissue taken from a pregnant woman is immoral, in that it constitutes an offence against human dignity to make use of a particular female condition (pregnancy) for a technical process oriented towards profit.
>
> (b) The patenting of human genes such as that encoding H2-relaxin amounts to a form of modern slavery since it involves the dismemberment of women and their piecemeal sale to commercial enterprises throughout the world. This infringes the human right to self-determination.

(c) The patenting of human genes means that human life is being patented. This is intrinsically immoral.

6.2 Before discussing the opponents' arguments, it seems opportune to take a look at Article 53(a) EPC and at the EPO Guidelines dealing with this Article. Article 53(a) states that European patents shall not be granted in respect of inventions the publication or exploitation of which would be contrary to 'ordre public' or morality, provided that the exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation in some or all of the Contracting States.

6.2.1 The provisions of Article 53(a) have only very seldom been invoked. While patent applications must be examined for compliance with all Articles of the EPC, including Article 53(a), the function of this Article has to be seen as a measure to ensure that patents would not be granted for inventions which would universally be regarded as outrageous. This interpretation is reflected in the relevant passages of the Guidelines (C-IV, 3.1). There it is stated that Article 53(a) EPC is likely to be invoked only in rare and extreme cases, for example that of a letter bomb. In addition, some general guidance is given as to when such a case might arise:

> A fair test to apply is to consider whether it is probable that the public in general would regard the invention as so abhorrent that the grant of patent rights would be inconceivable. If it is clear that this is the case, objection should be raised under Article 53(a); otherwise not.

6.2.2 Article 53(a) constitutes an exception to the general principle, set out in Article 52(1) EPC, that patents shall be granted for inventions which are industrially applicable, novel and inventive. The Boards of Appeal have repeatedly found that such exceptions are to be narrowly construed (see T320/87, [1] OJEPO 1990, 76, point 6 of the Reasons, and T19/90,[2] OJ EPO 1990, 486).

6.3 Turning now to the opponents' specific allegations relating to the present human H2-relaxin DNA, the patenting of the DNA would indeed be abhorrent to the overwhelming majority of the public if it were true that the invention involved the patenting of human life, an abuse of pregnant women, a return to slavery and the piecemeal sale of women to industry. However, the Opposition Division emphatically rejects these arguments.

6.3.1 With regard to the isolation of mRNA from tissue taken from pregnant women, the proprietor stated that the women who donated tissue consented to do so within the framework of necessary gynaecological operations. There is no reason to perceive this as immoral. Indeed, human tissue or other material, such as blood, bone, and so on, has been widely used for many years as a source for useful products, often proteins but now also RNA or DNA, which are unavailable elsewhere. Many life-saving substances (such as bloodclotting factors) are isolated in this way and many have been patented. Every evidence indicates that this practice is perfectly acceptable to and even welcomed by the vast majority of the public. Moreover, the use for other purposes of parts of the human body removed during the course of an intervention is explicitly approved in Article 13 of the Draft Bioethics Convention of the Council of Europe provided there are appropriate information and consent procedures.

6.3.2 The Opposition Division therefore agrees with the proprietor that there was nothing immoral about the isolation of the relaxin DNA. Contrary to the opponents' remarks concerning the repeatability of the invention, the isolation procedure need not be repeated in order to carry out the invention since a DNA fragment encoding human H2-relaxin can simply be chemically synthesised.

6.3.3 As for the opponents' assertions concerning slavery and the dismemberment of women, these are considered to betray a fundamental misunderstanding of the effects of a patent. A patent confers on its proprietor the right to exclude for a limited period of time third parties from commercially using the patented invention. It cannot be overemphasised that patents covering DNA encoding human H2-relaxin, or any other human gene do not confer on their proprietors any rights whatever to individual human beings, any more than do patents directed to other human products such as proteins, including human H2-relaxin. No woman is affected in any way by the present patent--she is free to live her life as she wishes and has exactly the same right to self-determination as she had before the patent was granted. Furthermore, the exploitation of the invention does not involve dismemberment and piecemeal sale of women. The whole point about gene cloning is that the protein encoded by the cloned gene--in this case human H2-relaxin –is produced in a technical manner from unicellular hosts containing the corresponding DNA; there is therefore no need to use human beings as a source for the protein. The

---

[1] Lubrizol/Hybrid Plants [1990] EPOR 337
[2] Harvard/Onco-Mouse [1990] EPOR 501

only stage at which a woman was involved was at the beginning of the making of the invention, as a (voluntary) source for the relaxin mRNA.

6.3.4 Finally, the allegation that human life is being patented is unfounded. It is worth pointing out that DNA is not 'life', but a chemical substance which carries genetic information and can be used as an intermediate in the production of proteins which may be medically useful. The patenting of a single human gene has nothing to do with the patenting of human life. Even if every gene in the human genome were cloned (and possibly patented), it would be impossible to reconstitute a human being from the sum of its genes. The opponents apparently do not object to the patenting and exploitation for medical purposes of other human substances such as proteins (even the H2-relaxin protein). However, no moral distinction can be seen in principle between the patenting of genes on the one hand and other human substances on the other, especially in view of the fact that only through gene cloning have many important human proteins (for example, erythropoeitin and the interferons) become available in sufficient amounts to be medically applied.

6.4 Besides the specific arguments set out above, the opponents also made broad statements regarding the immorality of patents on human genes in general. They maintained that patent applications relating to inventions in the field of genetic engineering cannot be treated the same way as applications relating to, for example, air pumps, but represent a special case requiring particular consideration under Article 53(a) EPC. They expressed the view that there existed among members of the public and all possibly concerned parties such as doctors, churches, and so on a consensus that human genes should not be patented, adding that only the EPO and the branch of industry concerned was in favour of patenting human genes. In this connection, the opponents also referred to the draft *Directive on the legal protection of biotechnological inventions* in the European Union (EU). The opponents insisted that the EPO should impose a moratorium on the granting of patents directed to human genes until this Directive has been implemented and not bring about a *fait accompli* in the meantime by granting patents such as the one under discussion.

6.4.1. The above argument completely ignores the current dispute within the EU (conciliation procedure) concerning the terms of the proposed EU Directive. While the European Parliament, of which the present opponents are members, has voted to prohibit the patenting of human genes in the Directive, the Council of Ministers is in favour of patenting isolated human genes and the 'Common Position' of the Directive adopted by the Council on 7 February 1994, explicitly allows this. No further evidence is required to refute the opponents' contention that only the EPO and industry are in favour of patenting human genes.

6.4.2 In view of the disagreement concerning the EU Directive, it is not clear at present what its final form will be and whether it will be in favour of or against patenting human genes. The imposition of a moratorium by the EPO on patenting human genes would in consequence be inappropriate and moreover impossible because there is no legal mechanism in the EPC for doing so.

6.4.3 As for the opponents' general assertions concerning the alleged intrinsic immorality of patenting human genes, these are founded on the premise that there is an overwhelming consensus among the Contracting States that the patenting of human genes is abhorrent and hence prohibited under Article 53(a). This assumption is false.

6.4.4 The disagreement between two bodies of the EU regarding the EU Directive (see above) perfectly reflects the current turbulent state of the public debate on biotechnology. Whether or not human genes should be patented is a controversial issue on which many people have strong opinions. Insofar as these opinions are often based rather on personal beliefs than on reasoned arguments, the discussion resembles those on other disputed questions such as abortion or the death penalty. Like the present opponents, many members of the public and other interested bodies appear to be against the patenting of human genes. However, their position is far from clear-cut since, as illustrated by the present proceedings, there is much confusion concerning the practical effects of a patent directed to a human gene. Properly informed on this point, those currently against such patents might well feel differently. Moreover, the view expressed tends to depend on the question being asked. For example, most people will probably say no if asked whether they approve of patents on human life; some may also reject the patenting of DNA encoding human proteins such as H2-relaxin. Nevertheless, the same people, if asked in the context of human health and well-being, will often approve of gene therapy, which, after all, necessarily involves a far more direct manipulation of human individuals than patents such as the present one could ever do. In view of this ambiguity, it may be concluded that the opinion of society on the question of patenting human genes is complex and not yet definitively formed.

6.5 Obviously recognising that the EPO is not the right institution to decide on fundamental ethical questions, the opponents requested that the EPO carry out a referendum to find out what the public in the Contracting States really wants to be patented. This request is refused since in opposition proceedings the burden of proof lies with the opponent--if they felt that such a survey might assist their case, it was up to them to carry it out. In any case, the Opposition Division wishes to point out that even if such a referendum were feasible, there is no provision in the EPC that only those inventions actively approved of by the public should be patented. If such a provision existed, it is arguable that the number of patents granted would be decimated since there are plenty of fields other than biotechnology (which the Opposition Division, unlike the opponents, does not see as a special case) in which patents may well be objectionable to parts of the public. Only in those very limited cases in which there appears to be an overwhelming consensus that the exploitation or publication of an invention would be immoral may an invention be excluded from patentability under Article 53(a).

6.6 In conclusion, neither does the opposed patent offend against widely- accepted moral standards of behaviour by promoting slavery, the sale of women, and so on, nor is there a clear consensus among members of the public in the Contracting States that patenting human genes such as that encodingH2-relaxin is immoral. In view of this, the patent is not considered to offend against Article 53(a) EPC.

Order

For the above reasons it is decided that the grounds for opposition do not prejudice the maintenance of the patent as granted. The opposition is therefore rejected in accordance with Article 102(2) EPC.

FOREIGN AFFAIRS AND TRADE

AUSTRALIA

AusAID the Australian Government's overseas aid program

Module Seven

Plant Breeder's Rights

Intellectual Property and Biotechnology

A Training Handbook

Contents: Module Seven

7.1 Objectives for Module Seven

This module addresses systems that protect and promote the development of new plant varieties. The terms *plant breeder's rights* (PBR) and *plant variety rights* (PVR) are commonly used to describe such systems and are used synonymously.

This module focuses on the most commonly used PBR system and other harmonised systems.

It also provides background on the aims of plant breeding, the relevant international and national PBR systems and the principal features of PBR.

By the end of this Module you should have an understanding of:

- How new plant varieties are bred
- The reasons to encourage the development of new varieties of plants
- The main features of a PBR system
- Relevant international standards and national PBR systems
- Alternative forms of protection

7.2 Introduction

What is plant breeding?

Plant breeding is the act of developing new varieties of plants through the transfer of desirable traits from parent to progeny, through the practical application of genetics.

Plants evolve naturally over generations through genetic variation that results from sexual reproduction and genetic mutation. The aim of plant breeding is to intervene in this process so as to ensure the transfer of specific desirable traits from parent stock to progeny. This involves changing the hereditary makeup of plants so as to fix the required traits in a stable form for successive generations.

The main techniques for plant breeding are selection, hybridization, genetic engineering and mutation:

- selection within a species allows for traits which can be inherited to be gradually reinforced in successive generations, by cultivating progeny only from those parents which best display the desired traits;
- hybridization entails cross-pollinating plants of different strains to bring together their desirable traits in their offspring. It is often combined with back-crossing and selection over several generations to ensure that the combined traits reappear in each new generation – to ensure that the hybrid 'breeds true' with the desired new trait;
- genetic engineering fast tracks the transfer of a desirable trait into the genetic structure of a plant; and
- mutations (or 'sports') occur naturally in plants, when the genetic makeup (normally of a single gene) spontaneously changes; in some cases this leads to an improved quality, which can then be bred further to produce a stable new variety including that quality. Radiation and chemicals can be used to induce mutations for use in breeding.

Public interest in plant breeding

Plant breeding in the past has produced the crops that are the mainstay of today's agriculture: for instance, what we know as wheat and corn are the product of many generations of selective breeding that created new varieties better adapted to meet humanity's needs. This process continues today, so that further plant varieties will be available to meet the challenges of sustainable agriculture, population growth and environmental impact, as well as providing other economic, social and cultural benefits for the community.

Plant breeding is particularly important for agricultural development around the world. New varieties are developed for agriculture for a variety of purposes, including for improving:

- productivity,
- quality and consistency,
- adaptation to diverse environmental conditions,
- flavour and nutritional value,
- resistance to diseases and pests, and
- properties useful in handling, shipping and storage.

Why have plant breeder's rights?

Any government that seeks to encourage the development and use of new plant varieties to bring about these benefits is faced with two basic questions:

- how to promote the availability of the necessary resources and investment for plant breeding to occur; and
- once useful new varieties are developed, how to ensure that their benefits can be enjoyed by society on reasonable terms, including the need for further plant breeding to continue.

One way to achieve this would be for governments to fund plant breeding directly, and this approach has been taken. But governments have also recognised the need to provide incentives for private plant breeders, or for institutes not fully funded by the government, to invest their resources in innovative plant breeding.

To this end, many countries have established a legal system of intellectual property (IP) protection known as 'plant breeder's rights' (PBR) or 'plant variety rights' (PVR). A PBR is a separate kind of IP right which is granted for a distinct new plant variety. A plant variety is generally defined as the lowest level of taxonomy (or classification) within the plant kingdom – in ordinary language, 'a group of plants that is distinct from all other groups of plants within a given species'. By contrast, a plant 'species,' a higher level of classification, covers plants that are different from one another, but are capable of interbreeding.

A PBR gives the innovator the opportunity, via a limited monopoly, to gain reward for their effort and investment. Without this period of exclusive rights, anyone else would be able to reap commercial benefits from the innovation without having to pay for its development. The innovator would have little chance of recouping the costs of creating the new variety, resulting in a major disincentive to investing in plant breeding and developing new plant varieties.

7.3 Legal options for PBR systems

PBR systems give plant breeders limited monopoly rights over the new varieties of plants which they create (see section 7.5 for the main features of a PBR regime). Although their subject matter is focused on plant varieties only, these rights are generally similar in their nature to patent rights (see section 7.6 for a comparison of PBR and patents): they do not amount to positive entitlement to commercialise the new variety, but give the right holder the entitlement to exclude others from doing a specified list of acts relating to the new plant variety. One key area where PBR systems differ from patent rights is in spelling out more clearly the exceptions to these rights, in areas that are important in the plant breeding industry – such as the entitlement of others to use the protected variety for research and further plant breeding.

Several legal options are available for plant variety protection:

- a specific legal system that is *sui generis* or tailor made for protecting plant varieties – commonly known as a PBR system;
- the patent system that encompasses plant varieties provided that they can be characterized as an invention and otherwise meet the normal criteria for patenting any new technology; and
- general legal mechanisms, such as protection of trade secrets and contract law.

Behind the acronyms – WIPO, UPOV, WTO, TRIPS…

In dealing with PBRs, you will see references to three international IP frameworks – the World Intellectual Property Organisation (WIPO), the International Convention for the Protection of New Varieties of Plants (UPOV), and the World Trade Organisation (WTO) TRIPS Agreement. WIPO, UPOV, and the WTO are separate Geneva-based international organizations with responsibility for different international agreements on IP, all of which have some bearing on plant variety protection. UPOV is the only one that administers a specific international system for plant variety protection.

- WIPO is responsible for many IP agreements including the Paris Convention for the Protection of Industrial Property, the Patent Cooperation Treaty, and the Berne Convention for the Protection of Literary and Artistic Works
    - It has no specific responsibility for plant variety protection, but deals with IP policy issues which have bearing on plant variety protection, e.g. biotechnology, access to genetic resources and traditional knowledge
- UPOV administers the UPOV Convention, and deals with detailed technical issues concerning plant variety protection
- WTO is responsible, among other things, for the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) which stipulates that IP protection must be provided for plant varieties. The TRIPS Council in the WTO is conducting a review of biotechnology IP, including a survey and comparison of the different approaches taken to protecting new plant varieties.

UPOV and WIPO work cooperatively together and UPOV shares its headquarters with WIPO in Geneva. By agreement with WIPO, the Director General of WIPO is also the Secretary-General of UPOV, although UPOV is a separate organization.

UPOV – the most common PBR system

The most common legal mechanism for plant variety protection is a specific PBR system. The *International Convention for the Protection of New Varieties of Plants* or, as it is normally called, the *UPOV Convention* sets out a framework for specific PBR systems that is used extensively. This model has very widely influenced the development of plant variety protection systems, including in many countries in the Asia Pacific region.

As with other international IP standards, the UPOV system is not a single template for national laws – instead, it is an agreed set of general standards which may be adapted and applied in different ways at the national level, making use of the flexibility within the system. This leads to national laws that express similar broad principles and can interact with other countries' systems, but that are adjusted to serve the specific legal environment and domestic interests of each country.

International standards often reach beyond the actual membership of the international treaty that create them: for instance, the classification system for patent subject matter created by the International Patent Classification (IPC) Convention is used almost universally throughout the world, even though relatively few countries have actually acceded to the Convention. Similarly, a number of countries have UPOV-consistent plant variety protection, even though they are not members of the UPOV Convention.

It would be possible to draw up and administer national laws on plant variety protection without regard to the international system, but this would have drawbacks. Why do governments choose to work within an international system, in particular the UPOV system?

Key elements of the UPOV system

UPOV establishes a number of principles that acknowledge the achievements of breeders of new plant varieties, by making available to them an exclusive property right, on the basis of a set of uniform and clearly defined criteria. A country which is either a member of UPOV, or has an equivalent system consistent with UPOV criteria, will normally be seeking some specific outcomes, such as to:

- achieve recognition that its plant variety protection system meets international standards, and gives effect to the TRIPS requirement of 'an effective *sui generis*' system;
- the ability of breeders to obtain protection in other member states under same treatment provisions;
- the ability of the breeders to claim priority in other countries for applications filed in the member state;
- make use of UPOV technical support for the examination of new plant varieties by use of UPOV technical standards; and
- the ability to influence the future implementation and development of international breeder's rights standards (especially through UPOV membership).

This is in addition to the general economic and social benefits expected from an appropriately balanced plant breeder's rights system. Governments seek to adapt and apply the general UPOV international standards in a specific national context in order to:

- encourage investment in plant breeding, and the transfer of technology and know-how from overseas;
- promote the development of varieties adapted to the nation's agricultural and economic conditions;
- establish a balance of interests between the breeder of a new variety and others who make use of the variety through further breeding or genetic modification;
- increase community access to varieties with improved characteristics of nutrition, productivity, taste, look, scent, and which alleviate some environmental concerns; and
- take advantage of harmonised international systems to facilitate the export of harvested material or end products produced from protected varieties, and trade in new plant varieties and technologies.

7.4 International standards and national systems

The main international IP agreement with detailed provisions for PBR is the *International Convention for the Protection of New Varieties of Plants* (UPOV). UPOV was established in 1961 and revised in 1972, 1978 and 1991. UPOV establishes harmonised international standards for plant variety protection, as well as mutual international obligations between parties to the Convention. The acronym "UPOV" is from the French name of the organisation established under the Convention, namely the *Union Internationale pour la Protection des Obtentions Vegetales (Union for the Protection of Plant Varieties).*

Prior to UPOV, plant variety protection developed in each country based essentially on national experience and requirements. This led to a patchwork of schemes which hindered trade and investment flows. The UPOV treaty was developed to promote protection on an internationally harmonised basis.

In September 2001, 49 countries were members of UPOV – from the APEC region, these include Australia, Canada, Chile, People's Republic of China, Japan, Mexico, New Zealand, and the USA. A number of other APEC economies have implemented PBR systems on the UPOV model without actually ratifying the UPOV Convention. Any country now wishing to take part in the UPOV system must accede to the latest revision of the Convention, the version concluded in 1991. Since a number of countries are still bound by the earlier 1978 version, a comparison of the two versions is provided below at section 7.7.

Almost all current PBR systems around the world conform with the standards of one of these versions of the Convention. In February 1999, the Office of UPOV advised that:

> … the only *sui generis* legal systems for the protection of plant varieties in any countries which were not based upon the principles of the UPOV Convention, were the plant patent system of the United States of America for the protection of asexually reproduced varieties and a similar system in the patent law of the Republic of Korea. The conditions for the grant of protection under these plant patent systems differ somewhat from the UPOV system. However, the effects of the two systems are similar and the United States of America first became a member State of UPOV on the basis of its plant patent law as a result of the enabling provision in Article 37 of the 1978 Act.

Also relevant to the exercise of PBR is the Convention on Biological Diversity (1994) and the work of the Food and Agriculture Organisation, especially the recently concluded International Treaty on Plant Genetic Resources for Food and Agriculture (see the discussion in *Module One).* The WTO TRIPS Agreement does not have detailed provisions on PBR protection, but stipulates that plant varieties must be protected by:

- patents; or
- effective *sui generis* protection, or
- both patents and *sui generis* protection.

All three of the above options have been exercised by various countries, although the clear trend is to implement *sui generis* PBR systems, whether or not patents are separately available. In the TRIPS context, *sui generis* protection refers to a system established specifically to protect plant varieties and nothing else (in contrast to patents which are for all areas of technology). The standards in the UPOV Convention are an example of the kind of effective separate (or *sui generis*) system required by TRIPS. A country could, theoretically, implement this standard by a system other than UPOV, although all the *sui generis* systems notified so far to the WTO are based on the UPOV model.

If a country chooses to protect plant varieties solely through the patent system, then new plant varieties would have to meet the general standards for patentability (novel, inventive, industrially applicable), as discussed in *Module Two: Biotechnology and Intellectual Property*.

In theory, countries can elect to develop their own PBR systems, with little reference to existing established systems in other countries or in international agreements. This was the situation internationally before the UPOV Convention was negotiated in order to deal with the problems created by incompatible or poorly harmonised national systems. Since UPOV was concluded, governments have generally chosen to take its international standards into account when setting up PBR systems. The obligation, under the WTO TRIPS Agreement, to provide some form of plant variety protection has also been a factor – while TRIPS does not mandate the use of a UPOV system, applying the established UPOV standards seems to be a widespread element in WTO Members' laws concerning plant variety protection.

There is a significant distinction between:

- implementing a national PBR law, which can give practical effect to UPOV standards (and can have additional provisions to deal with issues at the level), and
- formally joining an international treaty like UPOV, which sets general standards for national systems.

For instance, some countries elect not to join the UPOV system formally in the short term, but establish national laws that are in harmony with the UPOV model. This has policy benefits, and also has the advantage of facilitating adoption of formal UPOV obligations should that decision be taken at a later stage. Based on the decisions made by governments in this area, there appear to be three broad options reflecting differing levels of engagement with the UPOV system:

1. Acceding to UPOV 1991 (the latest version of the Convention), and adopting UPOV principles in domestic legislation that takes account of national interests.

2. Adopting UPOV principles without formally signing on to theUPOV Convention, gaining experience in their implementation, with the possibility of later joining UPOV when there is a separate decision that this is appropriate to national interests.

3. Adopting the core group of UPOV principles in national legislation – such as the definition of eligible new varieties – without any direct involvement in the UPOV system.

Each option leaves open the possibility of additional provisions in the national law to deal with specific domestic concerns and interests (provided that they do not conflict with the general UPOV principles). The UPOV system allows flexibility in how countries apply these principles as long as minimum criteria are met.

Examples of national systems for plant variety protection

People's Republic of China (PRC): The Regulations on the Protection of New Varieties of Plants is a UPOV based system. It provides for rights in new varieties of plants, which are defined as 'a cultivated plant variety, or a developed one based on a discovered wild plant, which is new, distinct, uniform and stable, and whose denomination is adequately designated'. Article 24 of the Patent Act of the PRC explicitly rules out the grant of patents for 'animal and plant varieties'.

Republic of Korea: Plants which are asexually reproduced can be protected under the Plant Varieties Protection Act. Under the Patents Act, a plant patent can be granted to a person who 'invents a new and distinct variety of plant which reproduces itself asexually.'.

Hong Kong, China: 'A plant or animal variety or an essentially biological process for the production of plants or animals, other than a microbiological process or the products of such a process' are not patentable under the Patent Ordinance. The Plant Variety Protection Ordinance provides for rights in respect of varieties that are 'new, distinct, stable, and homogeneous.'

New Zealand: Under the Plant Variety Rights Act, plant variety rights on the UPOV model are available for varieties of any kind of plant other than algae and bacteria. The word "variety" is used not in the sense of a "botanical variety" but rather as being synonymous with "cultivar" or "cultivated variety". The variety must be new, distinct, uniform and stable, and an acceptable denomination (variety name) must be proposed. Plants may also be covered by the patent system – for example, New Zealand patent 330495 concerns the 'cultivated dwarf olive tree free substantially as identified as Olea europaea 'DA-121' which is the progeny of female parent Olea europaea cv Dolce Agogia and male patent Olea europaea 'Pendulino'.

United States of America: The USA has three mechanisms that cover new plant varieties:

- the *Plant Variety Protection Act* provides for rights on the UPOV model to developers of new varieties of plants that are sexually reproduced (by seed) or are tuber-propagated, but not bacteria and fungi. Protection is granted if an examination shows that the variety is new, distinct from other varieties, and uniform and stable through successive generations

- under a specific plant patent system (under Chapter 15 of the *US Patent Law* (35 USC 161)), a plant patent can be granted to 'whoever invents or discovers and asexually reproduces any distinct and new variety of plant, including cultivated sports, mutants, hybrids, and newly found seedlings, other than a tuber propagated plant or a plant found in an uncultivated state.' Plant patents are only available to plants in the ordinary meaning of the word. Permitted forms of asexual reproduction include rooting cuttings, grafting and budding, apomictic seeds, bulbs, division, slips, layering, rhizomes, runners, corms, tissue culture and nucellar embryos.
- a plant that fits within the normal definition of a patentable invention can be granted a normal ('utility') patent of invention under the US Patent Law. For example, one well-known patent (partly reproduced in the exercises for *Module Two*), US patent 5,663,484 entitled *Basmati rice lines and grains*, was published with claims directed to:
    - a rice plant with certain defined characteristics,
    - a seed produced by this rice plant,
    - a rice grain derived from that seed,
    - a progeny plant of the claimed rice plant,
    - a rice grain with characteristics corresponding to the claimed plant, and
    - three related methods for selecting a rice plant for breeding or propagation.

7.5 The principal features of a PBR system

A PBR system is normally defined in separate legislation, such as the *Plant Variety Rights Act* in New Zealand, or the *Plant Varieties Protection Act* in the Republic of Korea. Reflecting its specialist focus, the PBR system is in some countries not administered by the industrial property office or patent office, but by specialist administrations, often within the government ministry or department concerned with agriculture. The European Union has established a regional Community Plant Variety Office (CPVO) in Angers, France, which administers a UPOV-style plant breeder's right system. It examines applications and issues plant variety rights that have effect in all EU member countries.

Since the UPOV standards are widely applied in national plant breeder's rights systems, this discussion of the principal features of a PBR system is based on the current version of the UPOV Convention, that is the 1991 version (as most national systems you would use in practice are based on the UPOV standard).

What is a 'variety'?

UPOV 1991 defines a "variety" as:

> a plant grouping within a single botanical taxon of the lowest known rank, which grouping, irrespective of whether the conditions for the grant of a breeder's right are fully met, can be:
>
> - defined by the expression of the characteristics resulting from a given genotype or combination of genotypes;
> - distinguished from any other plant grouping by the expression of at least one of the said characteristics; and
> - considered as a unit with regard to its suitability for being propagated unchanged.

What makes a variety eligible for protection?

UPOV provides that PBR may be granted to the "breeder" of a "new" variety that is:

- distinct,

- uniform, and
- stable.

The UPOV technical requirements for breeder's rights are referred to as the "DUS" requirements (from 'Distinct,' 'Uniform' and 'Stable'). This requirement is found in many national laws, and represents the most basic principle of plant varietyprotection.

Breeder

A breeder means the person who bred, or discovered and developed, a variety or an employee of the aforementioned person or a successor in title.

New

A plant variety is new if at the date an application is filed for a breeder's right propagating or harvested material of the variety has not been sold one year before the filing date in the country in which protection is sought. A plant variety is also new if at the date of filing for a breeder's right propagating or harvested material of the variety has not been sold four years before the filing date in member countries parties outside the member country in which protection is sought. In the case of trees and vines, the period is six years.

Distinct

A new plant variety is distinct if it is clearly distinguishable from any other variety whose existence is a matter of common knowledge at the time of the filing of the application (UPOV Article 7). UPOV also provides that an application in any country for a plant breeder's right or entering another variety in an official register of varieties makes that variety a matter of common knowledge from the date of the application. This is only on the basis that the application leads to the granting of a plant breeder's right or to the entering of the variety in the official register of varieties. This requirement ensures that the plant variety right does not interfere with the use of existing varieties.

Uniform

Subject to the variation that may be expected from the particular features of its propagation, a new plant variety is uniform if it is sufficiently uniform in its relevant characteristics. That is, within a specified environment, all plants of the population will conform to the description of the variety. In other words, when the variety is grown in the field, the great majority of individual plants must display all the specific properties that are claimed for the variety.

Stable

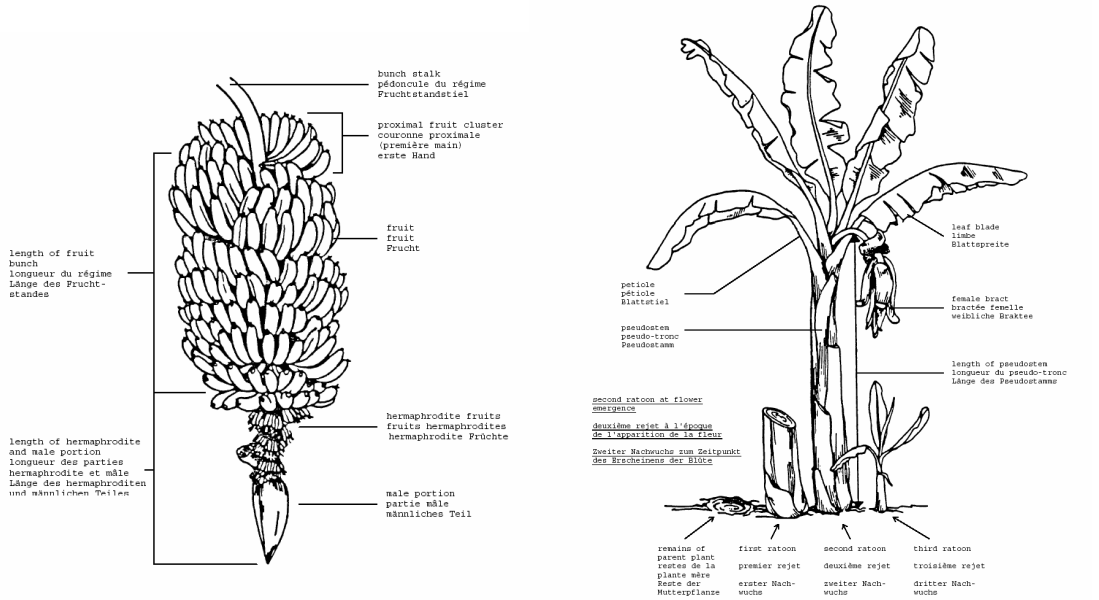
A new plant variety is stable if its relevant characteristics remain unchanged after repeated propagation or in the case of a particular cycle of propagation, at the end of the cycle. In other words, the claimed improvements or distinctive features in the new plant variety must not be a 'once-off' or transient property – they must be durable, and reappear in subsequent generations of the plant.

Examination

New plant varieties must be subject to a series of examinations before the grant of PBR can be made. While each country may have specific requirements, UPOV has an active role in harmonising national examination processes for assessing whether claimed new plant varieties meet the DUS requirement. This reduces the cost and uncertainty for breeders seeking protection in several countries, and assists administrations to apply their resources efficiently. Prior to the UPOV Convention, different countries had different examination standards for DUS testing. This lack of harmonisation caused problems for breeders who sought protection in different countries. The application of different examination standards also meant that a new variety might be granted PBR protection in one country but rejected in another.

The need for a harmonised system of examination guidelines for DUS testing has been addressed under the UPOV Convention. However even a high degree of harmonisation anticipates that interpretations may still vary between countries to suit specific national circumstances. To assist DUS testing UPOV has developed a large number of documents outlining the general principles of DUS assessment, which are summarized in the *General Introduction to the Guidelines for the Conduct of Tests for Distinctness, Uniformity and Stability and the Development of Harmonised Descriptions of New Varieties of Plants* (called the *General Introduction*). The UPOV Union also has developed individual *Guidelines for the Conduct of Tests for Distinctness, Uniformity and Stability* (the *Test Guidelines*) for specific genera which place the general principles in context. The number of Test Guidelines is constantly growing as protection is applied for in new crops. Test Guidelines are available at http://www.upov.int/eng/publctns/pdf/testguid.pdf

The principles set out in the General Introduction and the Test Guidelines give UPOV members a harmonised basis for testing new varieties and establishing variety descriptions in a standardized form. This information helps applicants for PBR protection as it informs them of the kinds of questions they will have to answer about their new varieties to get protection. The UPOV Test Guidelines also help cooperation between PBR authorities in different countries.



Extracts from UPOV document TG/123/3 of October 1989 establishing guidelines for the conduct of tests for distinctness, homogeneity and stability for the banana (musa acuminata colla)

UPOV requires that 'any decision to grant a breeder's right shall require an examination' to determine that the claimed plant variety is new, distinct, uniform and stable. It specifies that 'in the course of the examination, the authority may grow the variety or carry out other necessary tests, cause the growing of the variety or the carrying out of other necessary tests, or take into account the results of growing tests or other trials which have already been carried out.'

Two general approaches are taken to this form of examination (noting that the technical examination is distinct from the decision whether or not to grant rights). The examination can be undertaken by a central authority responsible for granting PBR, or it can be undertaken by separate institutions, such as public research institutes, acting on behalf of that authority. In some cases, the examination can proceed on the basis of growing tests carried out by the breeder or somebody employed by the breeder.

The result of the examination, including observations of the growing tests, is contained in the variety's description. The DUS characteristics need to be actively demonstrated before a PBR can be granted.

The applicant must also provide a suitable name for the new variety. This denomination should comply with detailed standards agreed upon by UPOV members. This includes ensuring that the new name is not confused with other indications commonly used in trade for the same or similar genera, can be reproduced and recognised, should not be available for other purposes, and are not protected in other ways (such as by trademark rights) that would hamper their use. The name should not be misleading, for instance in suggesting the variety has qualities it does not have.

Example – A new orchid

For example, imagine that a plant breeding business called "Oracular Orchids" had bred a new variety of orchid flower that had a unique cobalt blue colour, and had exceptionally long vase life. To get PBR protection, Oracular Orchids will need to demonstrate that the new variety meets the DUS requirements.

To prove the "distinct" requirement, this may entail comparing the orchid with the most similar varieties of orchid. This may include quantitative and qualitative differences between the new and the existing varieties. It can include morphological characteristics, which may be supported by comparative DNA or protein profiles. The differences from the existing varieties should be clear and repeatable. Performance (merit) attributes are not required though they may also be included if they can be precisely described and demonstrate that the orchid is distinct.

To prove the "uniform" requirement, the new orchid will need to be tested for variation, and only a very low level of exceptions to the claimed cobalt colouring and long vase life would be acceptable.

To prove the "stable" requirement, the new orchid will need to be propagated through successive generations to demonstrate that the claimed cobalt blue and long vase life continues to be present.

In addition, Oracular Orchids will need to come up with an acceptable denomination for the new variety. *Oracular* might be unsuitable, because it could be the company's trade mark – this would restrict others from using this name in the future. *Deep Blue* or *Livelong* might be considered too descriptive, because other breeders might wish to use these words to describe their varieties with these terms. *UPOV* would be unacceptable as it is the name of an international organisation. *Oceanic* might be an acceptable denomination, as a word only indirectly suggesting a deep blue colour – there would be no normal requirement for other breeders to describe their new plant varieties as 'oceanic'.

7.6 The nature of the Plant Breeder's Right

The plant breeder's right is an entitlement to exclude others from doing specific acts in relation to an eligible new plant variety. UPOV provides that in respect of the propagating material of the protected variety a breeder's authorization is required for the following acts:

- the production or reproduction
- conditioning for the purpose of propagation
- offering for sale, selling or other marketing
- exporting or importing, and
- stocking for any of these purposes.

More extensive or detailed rights may be granted through national legislation.

'Propagating material' can be defined as any product from which another plant with the same essential characteristics can be produced. For example, a rose can be reproduced by growing a bud or from a cutting.

The rights also extend to 'essentially derived varieties' (EDV), in other words, subsequent varieties that are derived from the protected variety and express all its essential characteristics. Essential characteristics" of a variety are the heritable traits determined by one or more genes or other heritable determinants that contribute to the main features, performance or value of the variety.

Essentially Derived Varieties

An important development in the 1991 UPOV standards is the introduction of the concept of 'essentially derived' variety. Protection under the more recent standards is extended from the protected variety to further varieties 'essentially derived' from it. This was developed owing to a perceived shortcoming in the earlier standards, particularly in the light of the new technology of genetic engineering. The UPOV web site (www.upov.int) describes this development as follows:

> Under the 1978 Act, any protected variety may be freely used as a source of initial variation to develop further varieties and any such variety may itself be protected and exploited without any obligation on the part of its breeder and users towards the breeder of the variety which was used as a source of initial variation. These rules have with certain exceptions worked well in practice and have been reaffirmed in the 1991 Act. However, the rules did not prevent a person finding a mutation within a plant variety (such mutations are quite frequent in some species), or selecting some other minor variant from within a variety, from claiming protection for the mutant or variant with no authorization from or recognition of the contribution to the final result of the original breeder. The lack of recognition of the contribution of the original breeder in such circumstances was generally considered to be unfair. Modern biotechnology has greatly increased the likelihood of such unfairness; it may take 15 years to develop a new variety but a mere three months to modify it by adding a gene in the laboratory. Under the 1978 Act, the addition of a single gene could enable the biotechnologist responsible for the modification to claim protection for the modified variety without recognizing any obligation to the original breeder.
>
> The 1991 Diplomatic Conference considered that this situation could be a disincentive to the continued pursuit of classical plant breeding. The concept of essential derivation embodied in Article 14(5) of the 1991 Act is designed to ensure that the Convention continues to provide an adequate incentive for plant breeding. Under that Article, a variety which is essentially derived from a protected variety and which fulfills the normal protection criteria of novelty, distinctness, uniformity and stability, may be the subject of protection but cannot be exploited without the authorization of the breeder of the protected variety. The 1991 Act contains a detailed definition of essential derivation. Simply stated, a variety ("B") is essentially derived from another variety ("A") when it (B) is predominantly derived from that variety (A), and except for the differences which result from the act of derivation, it (B) conforms to that variety (A) in the expression of the essential characteristics that result from the genotype or combination of genotypes of that variety (A). Accordingly, for practical purposes, varieties will only be essentially derived when they are developed in such a way that they retain virtually the whole genetic structure of the earlier variety. Any protected variety may, even under the 1991 Act, be freely used as a source of initial variation and, only if a resulting variety falls within the narrowly defined concept of essential derivation, is the authorization of the breeder of the protected variety required.

It should be noted that, while a number of countries have EDV provisions in their domestic legislation, there have been no legal challenges under such provisions and therefore practical experience with its effect is minimal.

Term of Protection for PBR

The minimum term of protection for PBR is generally 20 years, however for trees and vines the length of protection is 25 years (Article 19 in UPOV). The term of protection for trees and vines is longer than for other plant varieties in recognition of the fact that the breeding process for trees and vines is a much longer process than for other plants.

Exceptions to the breeder's exercise of PBR

UPOV also provides for mandatory exceptions to breeder's rights. These exceptions are for:

- acts done privately and for non-commercial purposes
- acts done for experimental purposes, and
- acts done for the purpose of breeding other varieties.

There is an optional limited exception in UPOV to allow farmers to save seed in UPOV), which many countries employ.

An example of administration of PBR - Australia

The system of protection for intellectual property employed by Australia is based on the UPOV harmonised system, the most widely used international system. It is implemented by the *Plant Breeder's Rights Act 1994* (PBRA) administered by the Plant Breeder's Rights Office located in the Department of Agriculture Fisheries and Forestry - Australia (www.affa.gov.au/pbr). In Australia, protection may also be available under the patent system for plant subject matter that meets other patentability criteria – so that plant varieties can fall within the scope of valid patent claims. Plants are excluded subject matter from the scope of the innovation patent (a form of limited protection of inventions of lesser inventive content than regular patents). The law of trade secrets may also be used by plant breeders – in one court case, for example, the propagation of a unique nectarine tree was held to be theft of a trade secret.

Australia has had plant variety protection legislation based on the UPOV 1991 system in place since 1994 but did not formally sign the 1991 Convention until 2000. In the interim Australia was able to promote its system as UPOV 1991 compliant and gain the benefits of increased investment and technology transfer (even though not formally bound by UPOV 1991). In a practical sense considerable experience with the concepts embodied in the PBRA was gained before Australia took the major step of acceding to the 1991 Convention.

In Australia, after a new plant variety is bred, an application for registration is lodged with the Plant Breeder's Rights Office. The characteristics of the variety are confirmed in a comparative growing trial, which is necessary to prove that the variety is distinct, uniform and stable. This stage is called "DUS testing". Australia uses a "breeder testing" model, which means that the applicant or an accredited person employed by the applicant conducts the comparative trial, records the observations and produces the variety description. The PBR Office makes an independent examination of the trial to verify the breeder's claims. The PBR Office publishes the variety description in the *Plant Varieties Journal*, which is distributed throughout the world (see below). Following a period for the public to raise any objection to the proposed registration of the variety, and if all requirements are met, the Registrar must grant PBR in the variety. PBR entitles the right holder, for a limited period, to exclude others from commercializing the plant variety and the propagating material of the variety. A certificate of grant is sent to the successful applicant and the Plant Breeder's Rights register is updated. The following is a hypothetical example of how an application is published for public scrutiny in the *Plant Varieties Journal*.

Example – Fantasy Pears

The Japanese Institute of Horticultural Research applies in Australia for PBR on a new variety of the Japanese Pear (*Pyrus pyrifolia*), called 'Fantasy'. It was a variation of the existing pear variety 'Reality', but is still in the same species, *Pyrus pyrifolia.* Protection for this variety has already been applied for in Japan, the USA, New Zealand and the Netherlands.

The origin of the variety is described: *Fantasy* was bred through deliberate mutation of nursery stocks of the variety *Reality* and selected for strong resistance to black spot disease.

The properties of the new variety are described, and compared to those of the 'closest comparator' – in this case, the original variety *Reality*. The results of field tests, focussing on resistance to black spot disease, are given as follows:

Fantasy	0% fruits infected	5-7% leaves infected
Reality	58% fruits infected	90% leaves infected

The Journal includes a colour picture of the two varieties showing their respective resistance to Black Spot.

7.7 A Comparison of PBR and Patents

Intellectual property in new plant varieties can be protected by a PBR system, by patents or by both. The advice of an expert in intellectual property law should be sought to determine the form of protection most suitable for the innovation and for the aims of the innovator. The choice of approach will obviously also depend on what legal systems operate in the countries you are interested in.

In some countries, patent protection is specifically excluded for new plant varieties and specific plant variety protection is only available under a UPOV-style system. For instance, this applies in the People's Republic of China, the Philippines, Thailand and a number of other countries in Asia. The pattern in Europe is also to deny dual protection. The EU Biotechnology Directive (see *Annex Three*) declares that plant varieties and essentially biological processes for producing plants shall not be patentable, although it provides that inventions concerning plants 'shall be patentable if the technical feasibility of the invention is not confined to a particular plant variety.' In these systems, PBR protection would be the only option if you wanted to protect a new plant variety as such (and not related technology, such as an inventive breeding technique, or products extracted from plants).

Some countries allow new plant varieties to be protected by both patents and PBR. For example, dual protection of new plant varieties is permitted in New Zealand, Japan, the US and Australia, provided the plant variety separately qualifies both as a new plant variety and as a novel, non-obvious, useful invention.

In highlighting the differences between the systems, the following discussion focuses on:

- the nature of the technique used to breed the new plant variety and whether the new plant variety satisfies the legal tests for protection
- the scope of the rights offered by the two types of intellectual property, and
- the examination process and registration costs.

Module Two: Biotechnology and Intellectual Property discusses the general characteristics of the patent system.

Protection for Intellectual Property in Plants

PBR and patents rights are similar in principle. They are both 'exclusive' rights – in other words, they give the right holder the entitlement to exclude others from doing certain acts. Generally PBR is more suited to the protection of new plant varieties as it specifically protects the end product of the breeding process: that is, the new plant variety in itself.

A patent can be granted for an invention that is new, involves an 'inventive step' and is capable of industrial application. A product or a process (or both) can embody the invention. If a new plant variety has been produced by an innovative technique or process, then it is possible that a patent could be granted for that technique and for the new variety produced by the technique. But this requires the breeding technique to be innovative in itself – it would not be enough for the plant variety to be novel.

If traditional breeding methods or standard genetic engineering techniques are used to produce a new plant variety, it may be difficult to establish that the variety amounts to a patentable invention – the techniques themselves would be part of common knowledge, and it would probably be obvious to use them in the search for a new plant variety. So even if these techniques required considerable effort and investment, the product they create may not amount to a patentable invention. A plant breeder's right would operate in this situation to provide an incentive and compensation for this effort and investment.

One of the requirements for patent protection is that the applicant must disclose the invention in sufficient detail to enable a person skilled in the art to perform the invention without additional inventive activity. If a new variety has been produced through traditional breeding, it may be difficult to detail how a plant variety can be reproduced with certainty given the mutability of plants.

The disclosure obligation also raises the question of whether the breeder's interests would be better served by keeping the breeding method or technique confidential and protecting it as a trade secret, especially as it may be difficult to 'reverse engineer' from a new plant variety the process that led to its development.

Scope of the Rights

Both PBR and patents rights of exclusion relate to the commercialization of the innovation in question. However PBR specifically allows for the innovation to be freely used for research purposes (with the goal of stimulating further innovation). The scope of rights granted by patent protection can be wider than those granted by PBR, for example, patents gives licensees the same rights as those of the IP owner. A patent could have the effect of covering breeding techniques and the new variety they produce, while a plant breeder's right cannot.

Examination Process and Costs

PBR is generally less expensive to apply for and to maintain than is the patent right. The examination process for PBR is usually less time-consuming than that for patents.

The following table summarizes the issues discussed above.

Comparison of PBR with Patents		
	PBR	**Patents**
Requirements	Novelty, distinctiveness, uniformity, and stability (DUS requirements)	Novelty, inventive step, capable of industrial application, and disclosure
Subject matter	Relates to a plant variety as such	An invention as defined by the patent claims, which could include a plant variety among other associated material (such as a new method of breeding which created the new plant variety) Plant varieties are excluded subject matter in many countries
Scope of right	Permits exemptions for research and breeding, and use of farm-saved seed for non commercial use.	May not have specific exemptions for non-commercial use of the patented invention (although exceptions for non-commercial research are generally well established)

7.8 A Comparison of UPOV 1978 and 1991

The current version of the UPOV Convention was concluded in 1991. The previous version, concluded in 1978, has closed, and countries can no longer accede to UPOV 1978. In September 2001, 18 countries were members of the 1991 Act, 29 were members of the 1978 Act, and two were bound by earlier Acts. This does not necessarily represent exactly the nature of national plant variety systems: a number of parties to the 1978 Act have laws which partly or completely conform with the 1991 Act, and a number of countries which are not members of UPOV nonetheless have national laws which apply UPOV principles. This section illustrates some of the key areas where the 1991 Act changed the standards in the earlier Act.

Scope of coverage

Article 3 of UPOV 1991 requires a member to apply the provisions of the Convention to all plant genera and species within five years of accession. This is an obligation additional to those accepted under the 1978 Convention. Under the 1978 Convention member States need only protect twenty-four plants and genera within an eight-year period following participation – in practice, members generally went well beyond this minimum level.

Scope of national treatment

Article 4 of UPOV 1991 requires a member to give the same treatment to other nationals as is given to its own nationals in respect of the grant and protection of breeder's rights. Under UPOV 1978, member States can limit the availability of protection for a genus or species only to the nationals of those member States offering protection for the same genus or species. This limitation is not possible under the 1991 Convention.

Right of priority

The UPOV system allows for recognition of 'right of priority' for applicants who have made an earlier application in another UPOV country. Under UPOV 1978, an applicant had four years to submit the necessary documentation to support a claim for priority. UPOV 1991 reduces this period to two years.

Scope of breeder's right

Article 14 of UPOV 1991 requires a member, subject to Articles 15 and 16, to make provision for the authorisation of the breeder in relation to the following acts in relation to the protected plant variety: production or reproduction; propagation; sale; selling or other marketing; exporting; importing; or stocking for any of these purposes. This effectively broadens the scope of the breeder's right from the earlier version. In UPOV 1978 the scope of protection is limited to production for the purpose of commercial marketing. UPOV 1991 extends this protection to cover all production, import, export or stocking.

UPOV 1991 also obliges a member (subject to specified conditions) to extend the breeder's right to harvested material obtained through unauthorised use of propagating material, when the breeder has not had reasonable opportunity to exercise their right in relation to the propagating material. It also provides an option to extend the plant breeder's right to products made directly from harvested material of the protected variety obtained through unauthorised use of propagating material, again when the breeder has not had reasonable opportunity to exercise their right in relation to the propagating material.

These changes were introduced because of practical considerations, such as the ability of an orchardist to propagate many hectares for years from one tree (thus potentially denying the breeder

reasonable commercial returns from a single sale of propagating material), and the development of technology which facilitates the rapid reproduction of plants. In addition, under UPOV 1978, the breeder's right does not extend beyond the propagating material to the material which resulted from the planting of the propagating material and the harvesting of the resulting crop. Some countries took advantage of this and exported back to the originating country the end product on which the breeder had not been rewarded and the grower faced unfair competition. The 1991 Convention provides the breeder with a right exercisable over the harvested material but only to the extent necessary to address the problems that arose in the past.

UPOV 1991 also requires a member to ensure that the breeder's right extends to varieties that are 'essentially derived' from the protected new variety, meaning that they, too, may not be exploited without the authorisation of the owner of the initial variety. This is in effect a clarification of the scope of the breeder's right. Under UPOV 1978, the breeder's right extends to the protected variety and, by implication to any variety that could not be easily distinguished from the protected variety. It also extended to any variety that was commercially produced by the repeated use of the protected variety.

Exceptions to the breeder's right

UPOV 1991 requires that the breeder's right not extend to acts done: privately and for non-commercial purposes; for experimental purposes; for breeding other varieties (subject to some exclusions). This is an explicit statement of obligations which are implicit in the 1978 Convention. This article also permits members to exclude from the scope of the breeder's right, the option of allowing farmers to propagate seed saved from their own harvest, so-called "farm-saved seed". The farmer's entitlement to use farm Saved Seed is not specifically permitted under UPOV 1978 but is expressly allowed under UPOV 1991, should a member wish to exercise the option to do so. The option is based on public interest considerations since the production and retention of seed is common practice for most field crops.

Duration of the right

UPOV 1991 requires a member to grant the breeder's right for a period of not less than twenty-five years for trees and vines and twenty years for other plants from the date of grant. This extends the duration of the plant breeder's right. UPOV 1978 allows member States to limit the grant of the breeder's right to eighteen years for trees and vines and fifteen years for other plants from the date of the application.

Cancellation of the right

UPOV 1991 gives a member the option to allow the cancellation of the breeder's right under specified conditions. This option is not present in UPOV 1978. It allows cancellation of the breeder's right subsequent to the grant of right if the variety does not continue to display the requirements of uniformity and stability.

Reservations

UPOV 1991 does not allow member to place reservations to the Convention, but does include the option for members to notify the Secretary-General of UPOV of its intention to allow title (patents) to continue for asexually reproduced plants. This option is additional to that permitted under the 1978 Convention.

7.9 Summary of Module Seven

What are some of the benefits of breeding new plant varieties?

- Improved productivity and quality of plants
- Plants to suit different climates and consumer requirements
- Plants adapted to different soils and resistant to diseases and pests.

What international agreements relate to PBR?

- The *Agreement on Trade-Related Aspects of Intellectual Property Rights, 1994* (TRIPS)
- The *International Convention for the Protection of New Varieties of Plants, 1991* (UPOV),
- The *Convention on Biological Diversity, 1994* (CBD), and
- The FAO *International Treaty on Plant Genetic Resources for Food and Agriculture* (2001).

What are the principal features of PBR under UPOV?

- PBR is the right to exclude others from doing specific acts (which are largely commercial acts) in relation to the new plant variety
- New plant varieties must be distinct, uniform, and stable (DUS)
- New plant varieties must be examined for compliance with the DUS requirements, the examination process may follow a centralised testing model or breeder testing model
- UPOV provides guidelines for DUS testing of different plant varieties to promote a harmonised approach to the examination of new plant varieties
- Exceptions to PBR are permitted for non-commercial purposes, and
- The term of protection is usually for 20 years but is 25 years for trees and vines.

Comparison of PBR and patents

- The nature of the technique used to breed a new plant variety is likely to determine whether the new plant variety satisfies the legal tests for PBR or patent protection. Generally, new plant varieties developed by traditional plant breeding techniques are more likely to be protected by PBR, and processes used to create new plant varieties using biotechnology techniques are more likely to be protected by patents.
- The scope of PBR is not as wide but is subject to fewer exceptions than that of patent rights.
- The examination process is less time-consuming and the registration costs are less for PBR than for patents.
- In some countries a plant variety can be protected by both PBR and patents.
- The advice of a patent attorney or commercial adviser will help determine whether PBR or patents is more appropriate for the new plant variety or technology.

7.10 Group Exercises - Module Seven

Module Seven provides information about PBR. Please discuss this Module with your fellow participants and prepare answers to the following questions.

Exercise 7.1 - Differences between UPOV, WIPO and the WTO

Dia is a soya bean grower in Malaysia. Over a period of 15 years she developed a new variety of soya bean using traditional plant breeding techniques of cross breeding. The new variety produced a higher yield than the previous varieties and was more appropriate for the climate in Malaysia. Dia was recently looking at the UPOV website. She is confused about whether UPOV is different to WIPO and the WTO.

(i) What does "UPOV" stand for, and why was it established?

(ii) What is the relationship between UPOV, WIPO and the WTO?

(iii) If Malaysia is a member of the WTO and WIPO, what options does that give her in seeking protection for her new variety in overseas markets?

Exercise 7.2 - TRIPS and PBR

Rano is an IPR adviser to the Indonesian Government. He has been asked by the Government to write a report outlining what Indonesia needs to do to comply with the PBR obligations in the TRIPS Agreement.

(i) Does TRIPS require members of the WTO to provide special protection for new plant varieties?

(ii) Which is the relevant article in TRIPS?

(ii) What options for complying with TRIPS could Rano suggest to the Indonesian Government?

(iii) Does TRIPS require members of the WTO to comply with the UPOV Convention?

Exercise 7.3 - PBR and international trade

Maya is an Australian plant breeder. She has been working to develop new varieties of citrus fruits to make the fruits juicier, easier to peel and ensure that they have less seeds. After years of breeding she develops a new variety of citrus fruit with these characteristics.

(i) Would she get intellectual property protection in Australia for her new plant variety of citrus?

(ii) What kind of protection would she get?

(iii) Maya wants to export her new variety of citrus plants to Singapore, to the People's Republic of China, to Hong Kong, China, to New Zealand, and to the US. What kind of intellectual property protection could she obtain in each of these countries?

Exercise 7.4 - Comparison of PBR and patents

Achmad is a Malaysian plant breeder. He has developed a new variety of cotton that is resistant to pests, particularly caterpillars. He pioneered a new form of genetic engineering in order to develop the new plant variety, and overcame problems that had been discussed in the scientific literature for some years.

(i) Should Achmad get patent protection for his new variety of cotton?

(ii) Should he get PBR protection along the lines of the PBR provided for in UPOV? Why?

(iii) Outline the different tests that Achmad would have to satisfy under UPOV to get PBR protection.

(iv) Outline the different tests that Achmad would have to satisfy under the TRIPS Agreement to get patent protection.

FOREIGN AFFAIRS AND TRADE

AUSTRALIA

AusAID the Australian Government's overseas aid program

Module Eight

Researching and Intellectual Property Rights

Intellectual Property and Biotechnology
A Training Handbook

Contents of Module Eight

8.1 Objectives for Module Eight

By the end of this Module you should have an understanding of:

- how to protect intellectual property while you are in the process of researching and creating your intellectual property
- how to prepare a combined intellectual property and research and development strategy
- when and how to use confidentiality agreements and material transfer agreements
- how to keep laboratory notebooks to prove when you make your invention
- what “freedom to operate” means
- how you make sure that you have freedom to operate before you commercialise your invention
- how to negotiate a research contract with commercial partners
- what clauses a research contract should have.

8.2 Putting intellectual property rights to work

Introduction to Modules Eight, Nine and Ten

Part Two of this Handbook (Modules Eight, Nine and Ten) covers the management of intellectual property (IP) rights from a more practical perspective than the earlier modules. This part of the Handbook considers the position of the biotechnology researcher in a research institute or in a university, and is prepared especially with the needs and interests of the researcher in mind. But this material is also intended to assist others working with technology or technology policy issues in the public or private sector. Many of the policy issues concerning biotechnology and intellectual property raise practical questions about the management and control of IP, at least as much as they raise legal questions about the definition of IP rights.

The underlying message is that IP doesn't exist for its own sake – it has to be managed actively to deliver the benefits expected of it. Well managed, it should support the goals of your organization or your research program; poorly managed, it can be costly without providing any substantial benefits. Part of good IP management is not letting IP take over – it has to be used in a way that contributes to what you are trying to achieve without becoming an end in itself.

There are many aspects to IP management, and this Handbook can only provide a general introduction. It doesn't cover some key issues such as valuation of IP – how do you put a monetary value on a patent or a trade secret? – or IP policies in the workplace – should employees be entitled to a share of patent royalties, and if so, who, and how much? Nor does it cover broader policy issues – should universities focus on pure research, aim at producing new commercial products, or both; what IP policies should apply to government-funded research? And the skills involved in negotiating technology agreements and licensing technology can only be developed through practice – and with the support of expert legal advice. But this part of the Handbook aims to give insights into some of the processes and practical issues that arise when new technologies are created and turned into useful products. So this discussion should assist in considering some of the broader policy issues.

Public and private IP management

Management of IP is often mentioned as part of commercialisation of research, but it can arise in a broader context. 'Commercialisation' suggests a specific private sector model of developing and marketing a new product or process, and using IP rights in a market environment. Yet IP rights may also be used by public sector institutions, without a specific commercial role, as a way of promoting the development, dissemination and uptake of their research. To some extent, the boundaries between the commercial and public sector models are becoming blurred. For instance, it can be difficult for a public research institute or university faculty to fund the extensive tests that are often necessary to make available to the public a new pharmaceutical, agricultural chemical or plant variety – at some stage, some form of financial support and external expertise will be needed. Often this kind of support is only practically available from the business sector. Potential business partners are likely to look closely at the scope and quality of IP rights before deciding to support a new technology. So in some cases IP management has been an important part of making a new technology available to the public, whether or not the research program has specific commercial motives.

For many people working in the biotechnology field, managing IP has become a practical necessity because the research tools they use are covered by IP protection, or they find they can't develop or apply their research outcomes in a particular direction without negotiating the use of another technology that is covered by a patent.

In any event, there are specific skills and legal mechanisms that are used to achieve the benefits of IP rights, whether these benefits are seen in commercial, developmental or social terms. Intellectual property rights can be a valuable resource, even for researchers involved in public research, but like any resource have to be carefully managed to produce the desired benefits. So a biotechnology researcher needs to understand how to manage IP, just as much as she needs to understand the principles of IP law. This Part of the Handbook therefore concentrates on these practical management skills and legal mechanisms.

- This module (*Module Eight*) looks at the research process, and some of the practical considerations that researchers have to take into account when their research involves IP rights – this Module looks in particular at the position of researchers in public research institutes or universities, but the same general considerations apply to other researchers as well
- *Module Nine* covers some of the practical considerations that apply when research outcomes are to be developed and put on the market, especially when this is done in association with commercial partners
- *Module Ten* provides some case studies on commercialisation of intellectual property in the biotechnology domain to illustrate how these considerations have been applied in practice, and to promote group discussion about approaches to IP management.

The pressure to patent - and some patenting myths

Some researchers are under increasing pressure to commercialise their research, because of a general shift in research policies towards more commercial models and because of pressures to find new sources of funding. This is behind the increasing interest in the patent system on the part of researchers, including those in public institutions. Patents are seen as evidence of effective commercialization. So researchers can sometimes feel they are under pressure to get patents for their own sake – just getting a patent becomes a valued outcome for its own sake, something to be achieved to demonstrate the commercial viability or other value of the research program. But this 'pressure to patent' can lead to some misconceptions:

- *A patent guarantees commercial returns.* Not so: in fact, a patent on its own doesn't itself lead to any financial benefit. Unless the patent forms one part of an overall commercialisation program or a broader IP management strategy, it could easily cost more money than any benefits it yields. IP protection can be necessary, but is rarely sufficient, for the successful development of a new technology.
- *Any new research outcome deserves a patent.* Not so. A patent is not like a publication in a scientific journal. Nor it is it a merit award for a research outcome that is highly interesting or admirable from a scientific point of view. It is not meant to serve a public accolade for a valuable contribution to scientific knowledge. For the inventor, the patent is a practical tool for managing a technology. (For many others, of course, the patent document *is* a useful source of scientific and technological knowledge – see *Module Four: Searching Patent Databases*.) The decision to get a patent is a significant step – scientific or technological merit is one factor, but the decision to go for a patent also has to make sense from the point of view of what the patent system is actually for – to facilitate and to give incentives to bring a new product to the market, or to assist more generally in the management of technology through commercial processes. That said, if the matter is in doubt, it may be wise to lodge a patent application just in case – if it turns out that there is no practical reason for pursuing a patent right, the application can be withdrawn early on, before the major expenses of patenting are incurred. If you at first don't file a patent application, and later change your mind, it may be too late.
- *A patent should just cover the initial research breakthrough.* Not necessarily so. If, as Edison suggested, genius is one percent inspiration, and ninety-nine percent perspiration, the patent has to cover more than that one percent of inventive brilliance – it has to cover some of the

practical effort required to put the invention into effect. A patent on an invention is not valid unless the patented invention is useful (or has 'utility'), unless the claims defining the invention are fairly based on the description in the patent document, and unless the description fully describes the invention, so that it can be practically put into effect. For some inventions, once the initial breakthrough is achieved, it is obvious how to put it into effect. But for most inventions, it often transpires that further experimentation and testing is needed after the initial technological breakthrough before a complete patent specification can be prepared that has sufficient description, and covers a form of the invention that corresponds with a realistic commercial product. Sometimes patent applicants file successive patent applications – one for the initial breakthrough, and later applications for improvements and extensions of the original concept – in many patent systems, these related patent applications covering the same inventive concept can be combined into a single granted patent.

- *Patents are just for major scientific achievements.* Not so. This misconception can deter researchers from exploring patent options because they assume patents are reserved for revolutionary advances in science. The great majority of patents are for relatively minor advances in their field, and for improvements on existing technologies. The requirement that a patented invention be 'inventive' does not mean that it has to create a new technology altogether. In fact, one way to negotiate 'freedom to operate' (the entitlement to use a technology someone else has developed) involves licensing your patented improvements back to the owner of the original patented technology.

Intellectual property – legal right or practical tool?

Part One of this Handbook (Modules One to Seven) concentrates on how intellectual property is recognized and defined as a set of legal rights. This is fundamental when working with technology - it can be vital to know whether an IP right is valid or not, and what the legal scope of the right is (see the discussion on patent rights in *Module Two* and on plant variety rights in *Module Seven*). The patent information system (described in *Module Four*) is important in locating what IP rights might affect your research activities, and can provides valuable legal and technological information for use in research and technology management. But to get benefits from the IP system, it is necessary to go further, and to discuss how IP rights are used as practical tools for managing technologies. In itself, a patent is an inert legal document – it can be expensive to get and maintain a patent, and it does not guarantee any financial return at all. The practical effects of a patent can depend on how the patent holder chooses to make use of it, and the relationship between the patent holder and other partners, such as research partners and commercial partners.

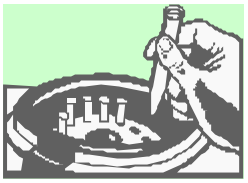
In some cases, if there is too much emphasis on exercising and defending patent rights to exclude potential users of the patented technology, this can lead to a self-defeating failure to build up valuable partnerships. Some patent holders have adopted an open licensing strategy – allowing anyone who wishes to take out a license to use the patented technology, for a suitable license fee (see the discussion of the Cohen-Boyer patent in *Module Nine*, for example.) Ownership of patents is not an end in itself – for some researchers or inventors, it can make sense to transfer the some or all their patent rights to a commercial partner, as part of a strategy to offload some of the costs and risks of managing the patent and to attract investment in the development of their invention. On the other hand, maintaining ownership gives the inventor a continuing say in how the invention is applied and used, and made available to the public. Flexibility and pragmatism are more likely to deliver benefits than pursuing and maintaining exclusive IP rights for their own sake.

In addition, patent law generally requires the patent holder to take active steps to make patented technology available to the public on reasonable terms. Under the patent law of many countries, failure to 'work' a patented invention, or attempts to use patents in an overly restrictive way can lead to the grant of compulsory licenses, which overrule the patent holder's exclusive rights. In extreme cases, a court might decide that the patent should be cancelled outright. So how you use a

patent (or if you elect *not* to use it) can be just as important as the process of getting the patent right in the first place.

8.3 Researchers and IP management

The research community needs to take account of practical management of IP rights, and development of partnerships involving the use of IP, for a number of reasons – firstly, to achieve your research goals, and secondly to ensure that your research outcomes can be made available to the public.



For the researcher producing new technologies, there is a danger that the patent process will become a burden, diverting attention from core research, taking up researchers' time and attention, and costing large sums of money – in the absence of a comprehensive strategy for dealing with the patented technology, this can all represent a major cost with no compensating benefit. Many patents are technically legally valid but give no tangible benefit to their owners. Indeed, many patents for useful technologies cease to have legal effect well before their term runs out, because the patent holder cannot afford to keep paying the renewal fees or has no commercial use for the invention. Research institutes rarely have the skills and resources to put a new product on the market, and to steer it through regulatory approval and other processes.

For the owner of a patent or trade secret, it may prove to be more beneficial to license others to use the technology ('licensing out'). The researcher and research institute are often better at creating new technologies and scientific insights than managing the process of putting their inventions into effect and directly commercializing all its possible applications. Otherwise, they can run the risk of mismanaging available resources – trying to convert skilled scientific researchers into entrepreneurs and business managers. This can have the effect of impairing research programs, while not delivering to the public all possible beneficial uses of the technology. But research institutes are often criticised for giving away their IP too cheaply, and allowing private commercial interests to reap the benefit of the public's investment in research. How to strike the right balance between maintaining control of IP and disseminating the benefits of research, while getting access to the resources you need to bring your inventions to the public?

Researchers or commercial enterprises also frequently need to make use of others' patented technologies to do their work, to develop and apply their own technologies, and to create useful products – the need for 'freedom to operate.' Technologies are increasingly interconnected and interdependent – this is especially so in the biotechnology sphere. A search of patent documentation might disclose a research tool, or a process, that will greatly assist you in achieving your research goals. It might be the only way, or the most efficient way, for you to do your work. It may well be that the technology is described in a European or US patent that is not in force in your country – which means you can use the technology in your country without legal problems (until you want to export to those other markets, at least).

But what happens if the technology you want is covered by a patent that is in force in your country? Patent law often allows for exceptions for pure research, so that if you need to use another parties' patented technology for scientific research, you may be able to depend on such an exception (although you should always check the exact legal situation before relying on this). And this kind of exception doesn't help once you go beyond the research phase, and you need the other patented technology to make the new technology you have produced available to the public. This is normally achieved by getting a licence for the patented technology ('licensing in') from the holder of the patent, allowing you to use the patented invention for specific purposes. Don't assume that a patent is a complete barrier to your own activities. The patent holder may see (or may be encouraged to see) the benefit in allowing their technology being used in diverse applications. Again, if a patent holder fails to make the patented technology available on

reasonable terms, many countries have provision for compulsory licenses to ensure that the technology can be used for the benefit of the public.

For those who make contributions towards the development of new technologies, such as the provision of intellectual capital in the form of traditional knowledge or other background intellectual property, facilitating the development of the new technology through providing access to unique genetic or biological resources, the patenting of the technology in itself provides no direct benefit. Indeed, some commentators on the patent system suggest that it should take more account of such contributions.

One vital practical tool for achieving this is a contract or agreement covering the use of this background contribution – typically, the contribution can be recognized by a direct payment and by some form of share in the commercial benefits of the invention; the agreement can also offer access to the patented technology itself. Research agreements, material transfer agreements, and information transfer agreements, are some of the legal tools that are used.

In each of these situations, the practical solution does not lie in the patent document itself, but in the way the patented technology is managed – most frequently, the mechanism for doing this is some form of agreement or license. In most practical scenarios, reaching agreements and licensing arrangements for the use of patented technology is at least as important in getting benefits from technology – at the individual level, and at the level of society – as the nature of the patent itself.

Cooperative structures for technology management

Few innovations can now be fully researched and developed, and manufactured and marketed internationally as new products, without a wide range of relationships – this is especially so in the biotechnology field. No one institution, especially a research or educational institution, is likely to have all the skills and resources necessary to achieve commercial success with an innovation.

Agreements and contracts will determine how you share the risk with others, make use of others' skills and resources (technological, industrial, financial and commercial), and keep your fair share of the benefits that derive from the invention. They can also determine how your technology is put into effect and used for the benefit of the public.

In the biotechnology field – for instance, in the development of a new pharmaceutical or a new plant variety – the cost of getting health, safety and environmental approval from the regulatory authorities can be very high, and this is a cost that must be borne before the new product can be put on the market – in other words, before there is any income at all. For a research-based institution, especially, or even a small or medium commercial enterprise, it is often necessary to enter into a partnership with another company to share the financial and administrative burden of getting approval for a new product. Management of IPRs is an important part of any such arrangement.

In short, gaining intellectual property rights is a valuable first step; but effectively managing those rights is even more important, whether your motives are commercial, for the broader public interest, or both.

8.4 How do IP rights affect researchers?

Why should one have to take account of intellectual property rights while they are researching? Most researchers working in the biotechnology field find they need at some time to consider IP issues, even if they are not working in a commercial environment, and even if they are engaged on fully-funded research for the public benefit. For example, if you are working on a new technology, you will need to consider:

- Can your innovation be put into effect in public without the use of others' IP rights – for example, have you used an enabling technology in your research that might limit the full-scale use of your innovation? Does your innovation itself make use of someone else's patented technology?
- Can you make use of others' research to increase your chances of success? Would this be helped by some form of research or commercial partnership, by cross licensing or technology pooling? Would this be more effective than creating a new product completely on your own?
- Would it be important for you or your research institution to have a say in the development and further exploitation of the research? Could you use IP rights to ensure the future directions the technology might take?

In these situations, effective management of your own IP rights opens up opportunities other than directly commercializing an innovation and generating royalties. IP rights over your research can be used as a bargaining chip in gaining access to other technology, and in influencing how downstream developments from your technology are applied. At the same time, research institutions can make use of IP rights to generate income to support their further research activities, in a climate of rising investment costs and limited public sector funding. The pressure on research institutions to broaden their funding support is another reason for effective IP management in relation to their research programs.

It is therefore very important to think about protecting your intellectual property while you are still researching. Unfortunately, some researchers lose their valuable intellectual property rights because they do not think about intellectual property until after they finish their research and development. This is usually too late!

Researchers need to follow several steps to protect their intellectual property rights while they are researching:

- know how intellectual property rights can protect their research,
- develop a research and development strategy that addresses intellectual property issues,
- know how to use confidentiality agreements and material transfer agreements to their benefit,
- keep good notebooks to prove the date of the invention, and
- get specialized intellectual property advice early in the research.

Each of these points is discussed below.

It is not sufficient, however, for an individual researcher to be aware of these considerations. For an institution, there are several important management considerations that may need to be addressed in establishing a research program. These include:

- promoting a culture of innovation,
- establishing confidentiality rules and procedures, including staff awareness programs, and briefings for staff on recruitment and separation, and documentation such as standard non-disclosure agreements and employment contracts,

- establishing procedures for identifying and safeguarding potentially patentable material, including laboratory notebooks, and forms and procedures for reporting research outcomes,
- establishing a publication policy which balances the need for preserving patent interests with the researcher's and institute's interest in publication of research outcomes, and
- establishing an objective decision-making process, such as a patent committee, for determining whether to pursue patent protection, and for considering patenting strategies.

Even research institutions that operate wholly in the public sector, for the broader public benefit, are considering the strategic management of potential IP rights in order to achieve public benefits. Not all IP management is aimed exclusively at developing a commercial advantage. Other considerations can include:

- Maintaining direction over the further use and application of technologies that a public research program produces, and keeping open access to the technologies. This applies especially when others develop and apply the technology, and make improvements to it in the process of bringing the technology to the market. Keeping control over the basic technology through IPR management can actually give stronger guarantees that all those who stand to benefit from the new technology can have reasonable access to it. Failing to secure and exercise IPRs on the original technology can actually have the unintended effect of restricting access to the new technology as it's applied in practice.
- Gaining leverage over other technologies necessary for the implementation of your technology – you may need to use technologies that are protected by other parties' IPRs, and you can use your own IPRs to reach a cross-licence or another form of agreement to gain access to that technology (using IPR to negotiate 'freedom to operate')
- Enabling the investment of resources required to bring the technology onto the market, such as clinical tests or field trials and the development of data packages required for regulatory approval, as well as any further technical development needed to turn the technology into a useful product
- Supplementing or diversifying the income required to fund public sector research, through a royalty stream or direct investment in a research program. This may also be important in attracting and retaining key personnel, and reversing the 'brain drain.'
- Using public sector technology development as a way of building up a critical mass of technology management skills, so as to enhance the national skills base and its strategic capacity to develop and apply useful new technologies.

8.5 IP awareness and research

Module One: Introduction to Intellectual Property gives an overview of the kinds of intellectual property rights that are relevant to biotechnology, for instance in supporting the commercialisation of new technologies. Patents can protect research results, methods, sequences, vectors, living cells and organisms (including plants in some countries), provided they meet the standards for a patentable invention. Plant breeders' rights protect new varieties of plants. Trade secrets (undisclosed or confidential information) can protect your research results, know-how, and methods if they are disclosed in confidence. Trade marks are signs that distinguish goods and services from the goods and services of other traders. Trade marks help you to establish and maintain your business reputation that can be very important in commercialising your research.

Module One also describes how you may need to take account of the intellectual property system at each stage in a research and development program. At the very first stage – planning the direction of a research program – a patent search is a valuable step to take, firstly in ensuring that you are not planning to do research that has already been done, secondly to learn from the complementary research outcomes of others, and thirdly to assess whether you will have the necessary freedom to operate when it comes to commercialising the outcomes of your research. See *Module Four: Searching Patent Databases* for details on patent searching.

How to get a patent - the patent process

Module Three: Reading a Biotechnology Patent and the Patent Process sets out the process that you may need to follow to get patent rights, remembering that each country may have a slightly different process. Patent rights are granted in return for disclosing the best way to work the invention. *Module Two: Intellectual Property and Biotechnology* outlines the tests that an invention must satisfy to get a patent. In summary, an invention must be new, involve an inventive step and be capable of industrial application. In summary, you need to:

- seek expert advice early in your research from a patent attorney or commercial adviser. Your research institution or employer may have in-house expertise in this area.
- search for prior art. That is, you need to search patent databases and other sources of information to find out if your research has already been done – this process is described in *Module Four: Searching Patent Databases*
- decide if patenting, or other IP protection, is appropriate for your invention. A commercial adviser or patent attorney can help you to make this decision.

Research institutions generally establish internal policies and processes for assessing and making decisions on patenting. The early decisions made on patenting are often the most important, particularly because any choice not to seek a patent can be difficult or impossible to reverse later on. At the same time, the decision to take out a patent is a business decision involving significant investments, and it is often considered that the individual inventor alone or the research team is not in the best position to make the decision – a collective decision, according to an established patenting policy can be preferable.

What rights does a patent give me?

A patent owner is entitled to exclude others from commercially practising their invention as described in the claims. A patent is limited to the jurisdiction of the country or region in which it is issued, so doesn't apply to acts in other countries. And there are exceptions to patent rights in many countries, which allow others to use the patented invention for research and education, and potentially other non-commercial uses.

The patent doesn't give the right actually to use the invention. In other words, just because you get a patent doesn't mean you can put your invention on the market. First, there may be other

patents in force which cover the background technology, so that your patent couldn't be exercised without infringing those other patents. Second, there may be government regulations which restrict the exercise of your invention for environmental, safety, health and ethical reasons.

When can I publish my research?

Be careful! The need to get a patent doesn't mean you can't publish your research or discuss it with your scientific peers in the normal way – but it can mean delaying any kind of disclosure of your invention before you are sure of your legal position. In particular, if you are interested in patent protection, you need to get legal advice before you publish your research. This includes publishing your work in a journal, describing it in a conference or seminar, or demonstrating it in public. You should not publish your research in any of these ways before you apply for a patent. There are a few limited exceptions to this rule (known as 'grace periods') in some national patent law, but in general you should not rely on an exception being available.

If you do publish before a patent application is filed ('prior publication'), then you probably won't be able to secure a valid patent for your invention, because your own publication will be considered prior art which means that your invention was not 'novel' when a patent was applied for. Even if the prior publication is not found by the patent examiners and a patent is actually granted to you, your patent is likely to be found invalid if it is ever challenged by a third party (for instance, if you had to enforce it against an infringer).

Once your patent application is filed, then you are free to publish, demonstrate and indeed commercialise your invention. In fact, the patent application itself will be published in due course (unless you withdraw it) and will itself constitute a useful source of information about your invention for others. The very basis of patent rights is that exclusive commercial rights are given to inventors for a limited period of time in return for disclosure of the invention.

There is still a need for caution, however. If you come up with improvements and developments of the invention after the invention is published, it may be impossible to get patent protection for this additional material. The earlier publication of your invention may make the improvements ineligible for patent protection, on the grounds that they are obvious in the light of your invention. In any case, you should be careful *what* you disclose after your patent application is filed – if what you describe or publish goes beyond what is disclosed in the patent application, you may lose rights to get patent protection for that additional material.

Scientists and researchers generally have a strong commitment to publishing and discussing openly their research. The desire to publish research results and the requirement to maintain a level of discretion on the timing of publication can create some tension between researchers and commercial interests. Through early inclusion of an IP strategy in a research program, this tension can frequently be negotiated.

8.6 Combining research & IP strategies

As researchers, you need to integrate your intellectual property strategy with your research and development strategy from as early on in the research program. This will maximise the commercial benefits that may derive from your hard work. Intellectual property management issues arise at every stage of research, from planning, through to research outcomes and the completed product in the market. See 'IP and the lifecycle of a new product' in *Module One*.

The following table sets out how R&D issues are aligned with IP management issues as the research proceeds from research, to product development, to commercialisation.

	Research	Development	Commercial
R & D Strategy	• set objectives	• test with other systems	• seek partners
	• identify milestones	• check the stability of outcomes	• negotiate agreements
	• develop strategies	• select best prototype	• establish licences etc
	• research, experiment, repeat, review, generate outputs	• optimise performance	
	⇕	⇕	⇕
IP Strategy	• check that your research has not already been done (i.e. check "prior art")	• check prior art again and check third party positions	• maintain intellectual property rights
	• locate third party rights	• negotiate when appropriate with third parties	• pursue infringers
	• decide whether to make or buy the technology you need	• revise IP protection strategies	• monitor competitors
	• protect IP as it arises		

(table courtesy of Cheryl McCaffery, EclIPse, and Carol Nottenburg, Cambia)

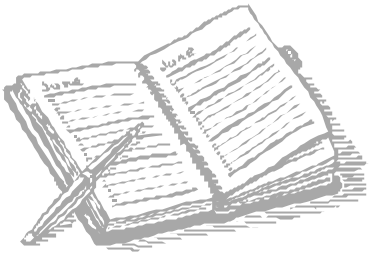
It is important to combine an IP strategy into your research planning from the outset. For example, if you check prior art early in your research process you might find that your research has already been done, or that the research direction you have chosen is not the best way of achieving your goal. Such a prior art search could save you wasting your valuable time and money. A prior art search might also give you ideas for different research projects that build on existing technology. *Module Four: Searching Patent Databases* sets out where and how to search databases to check for prior art. A search will also help you to identify freedom to operate issues in the event that technology upon which you're building is already protected by a patent. The above table shows how checking prior art and the position of third parties is a recurring process. The section below on *Freedom to Operate* covers particular aspects of this process.

8.7 Research practicalities

This section covers some of the practical management issues you may confront as a researcher or as the manager of a research program.

Keep laboratory notebooks to establish the date of your invention

As discussed in *Module Two: Biotechnology and Intellectual Property*, most countries follow the first-to-file system, meaning that the effective legal date attached to the patent is, generally, the first date a patent application is filed in the patent office. But the 'first to invent' system of the United States means that it can become very important to provide evidence of when the invention was actually conceived and reduced to practice. For this purpose, it is standard procedure to maintain detailed laboratory notebooks in order to safeguard patent protection in the United States. The laboratory notebooks do not have to be submitted with the patent application, but are drawn on as evidence in the event that there is a conflict between the patent claims in your application, and those of another patent applicant. This arises in 'interference' proceedings in the US Patent Office, when the office seeks to decide between competing claims to the same subject matter.



The notebooks should provide strong evidence of *when* two key steps occurred, the *conception* of the invention and its *reduction to practice.* The conception is the initial idea or conceptual breakthrough; the reduction to practice is the process of turning the initial idea into a practical, working form. It should also show the researchers' *diligence* in proceeding from conception to reduction to practice – in other words, it should show that the researchers were continuously active in reducing their initial idea to actual practice. This is because, in deciding between competing claims to the same subject matter, the US practice is to give priority to the first conception of the invention, provided there has been diligence in reducing it to practice. US Patent rights could be lost to another claimant, on the other hand, if there was initially no attempt to follow up the conception and put it into practice, and the other claimant meanwhile conceived their invention and diligently reduced it to practice.

You should seek detailed legal advice on this aspect of United States patent law, and build it into the management of any research program that aims at developing a technology that may be patented in the US. To illustrate the kind of approach that is necessary, some general considerations are mentioned here.

Apart from their value in establishing priority in the US, laboratory notebooks may be helpful in general management of the research program – for instance, in keeping track of research data, preparing scientific publications, complying with record-keeping requirements as part of a research agreement (including confirming when research milestones have been reached), drafting a patent application, ensuring important information is not lost with staff turnover, and demonstrating compliance with government or university guidelines for laboratory practice.

A key legal requirement for keeping notebooks is the witnessing of the lab notes. Don't forget the notebooks may have to provide convincing, objective evidence in a court of law. This means that another person who can understand your work, but who is not directly involved in your research, must regularly witness all entries and be prepared to sign your lab books.

Guidelines for keeping lab notebooks

The basic objective of keeping the notebook is to provide convincing evidence that the experiment did produce the claimed invention, and on the date that is claimed as the date of invention. Many of the specific requirements flow from this general goal. Following are some basic guidelines for keeping lab notebooks will help you prove the date of your invention. If you have significant plans for securing US patents for your work, your research record-keeping practices should be checked against authoritative legal advice. The guidelines for keeping lab notebooks should generally include:

- use of bound notebooks (not loose-leaf)
- numbering of each book sequentially, and numbering each page
- storing books securely
- detailed description of your hypothesis, experimental design, materials, methods and results, with as much specific information as possible, and clear cross references to related work in other notebooks
- permanent fixing of all labels, print-outs, photos and scans into your notebook
- recording of each entry in permanent ink
- drawing a single line through errors, **not** erasing entries
- using every page in your notebook, and filling any gaps
- do not remove pages or portions of a page
- if you do not work on a project for a period of time state the reasons why and indicate the page number in your notebook where the next relevant entry is
- recording of all experiments, including those that fail
- signing and dating each entry or experiment on an daily basis, and
- getting someone who did not perform the work (but who understands the work) to read and sign the new work on a regular basis, eg, "Read and understood by:_____" write the person's name and date the entry.

Computers should not normally be used as your only notebook because the data can be too easily altered, and it is less convincing as evidence. Computer-stored data might be enough to establish a date of invention only in limited cases. For instance, computer stored data can be persuasive if the data are printed out and bound shortly the time of creation, and this printout is signed and dated by the person who created the data and is witnessed by another person. If you are planning to use electronic data systems as your principal laboratory notebook, you should seek up to date legal advice on the best approach to take.

Working with legal agreements

The researcher will often have to deal with other legal documents that involve the use of IP and similar rights. These include:

- confidentiality (or 'non-disclosure') agreements (as part of a research collaboration, for instance, or even as a condition of employment),
- licensing agreements (such as agreements to license the use of research tools and other technology), and

- material transfer agreements (for example, when obtaining germplasm or plant propagating material in their research, or getting access to genetic engineering tools such as vectors or cell lines).

In addition, the research may be covered by a research agreement, for instance with a funding agency or a commercial partner. These agreements involve two practical skills – first, how to negotiate the right deal, so that the agreement represents an arrangement that is fair and workable; second, how to understand and interpret the text of these agreements. Section 8.9 of this Module, and *Module Nine: Licensing and Enforcing Intellectual Property Rights* discuss these agreements in more detail.

Seek expert advice

Patent attorneys (or patent agents), other legal practitioners and commercial advisers can provide you with help about patenting and commercialising your research. Your government patent office can also provide you with information about the patenting process and use of patent information systems.

A patent attorney (or patent agent) can:

- help determine if your invention is patentable,
- advise on the validity of patents owned by commercial partners or rivals,
- advise you on whether you might infringe third party IP rights,
- manage the patenting process in your country and in foreign markets, and
- help you to resolve ownership and inventorship issues.

A legal practitioner can advise on:

- the nature and effect of legal agreements,
- rights of employees, students, contractors and other participants, and
- the regulatory environment, for instance in getting necessary licenses and approvals.

A commercial adviser can help you to:

- value your invention to prepare for commercial negotiations and financing arrangements
- manage relationships between you and your commercial partners, and
- negotiate contractual arrangements.

8.8 Freedom to Operate

Many biotechnology inventions require the use of existing technology. Even if you get a patent for a particular new biotechnology product, you might have to use existing technology to commercially exploit your new product. Your patent doesn't give you an automatic right to commercialise your invention. Other, existing patents (for instance, covering the genetic engineering techniques you have used to create your new product) might stand in the way. Before you commercialise your patented invention you need to make sure that you have 'freedom to operate.' This means that ensuring that the commercial production and marketing of your invention does not infringe the intellectual property rights of other people.

What is "freedom to operate"?

Freedom to operate means that you are able to work your invention without hindrance. That is, you can market your product without infringing the rights of other patent owners. It is important to remember that a patent is not a positive grant to exploit your invention. As the owner of a patent you have the right to exclude others from working your invention. Even if you have a patent for your invention you might need to use another person's patented technology. In this case you will need permission from that owner to use their technology. Having all the necessary permissions to practise your invention is called "freedom to operate." There are two, complementary aspects to getting freedom to operate:

- the technological pathway – determining the technology that is needed to exploit your invention as a commercial product in the marketplace
- the legal pathway – determining how to avoid infringement of legal rights pertaining to the necessary technology

You might secure freedom to operate by avoiding existing patent rights (either by choosing an alternative technology, or by staying out of a market where the patent is in force), by negotiating a licence with an owner of key technology, or even by forming an alliance or partnership with the technology holder. The technology owner might have a commercial or strategic interest in working with you, and may be able to provide additional know-how and background intellectual property that will make your invention all the more commercially feasible and technically successful.

How to check for freedom to operate?

There are a number of steps that you can take to ensure freedom to operate in the field of patents, normally with the assistance of a specialist on patent law who is familiar with your field of technology:

- make a list of all the technologies used in your invention and any other relevant information
- carry out patent searches
- identify potentially relevant patent specifications
- find out all the countries where relevant patents are filed, that is, find the extended "patent family"
- obtain copies of relevant specifications and claims
- ascertain the legal status of each relevant patent application
- seek the assistance of a patent attorney to understand the claims
- establish whether your activity would infringe the claims of existing patents

- check the legal status and the term of the patent grant (for example, the patent might have expired; or it may have lapsed or been cancelled before the patent term ends), and
- seek the licence, that is, the permission, of the patent owner, if needed.

Be careful with the last step of seeking the permission of the patent owner. The timing of doing this is critical. If you do it too soon you may pay for something that you do not need, and better technological solutions may be available by the time it comes to commercialising your patent. If you seek permission of the patent owner too late you risk being denied access to the technology you need and be sued for patent infringement! You will need to get advice from a patent attorney or commercial adviser about seeking a licence to use technology from existing patent owners.

If you are dealing in plant varieties – for instance, if your invention involves use of plant germplasm (see the Bt cotton case study in *Module Ten*) – you may also need to consider freedom to operate from the point of view of plant breeders' rights. You would need to consider:

- does producing your variety require repeated use of another variety?
- is that other variety the subject of a grant of PBR?
- if so, in what countries have the PBRs been granted?
- according to the laws of those countries, what is the scope of the PBRs? and
- will you market your product in those countries? (if you do you might be subject to their rights).

There is a second broad issue you need to consider to determine if you wish to market a new plant variety without infringing existing plant breeders' rights. This issue relates to "essentially derived varieties". In countries which have laws along the lines of the 1991 version of UPOV (see the discussion of this issue in *Module Seven*), existing plant variety rights may cover new varieties that are essentially derived from the protected variety. In that case, you may need to ask yourself the following questions in relation to your new plant variety if it is potentially an "essentially derived" variety:

- what variety did you transform?
- who "owns" it?
- do they have a grant of PBR?
- if so, in what countries?, and
- will you market product in those countries? (if you do you might be subject to their rights).

Please see *Module Seven: Plant Breeders' Rights* for more detail on plant breeders' rights, including details of the scope of the plant breeder's right and its potential coverage of essentially derived varieties.

Other IP rights and freedom to operate

Freedom to operate issues are not limited to patent rights or plant breeders' rights, although these are naturally the main focus of concern in relation to biotechnology. Depending on the nature of your research and your plans to develop it, there may be other IP rights that need to be considered – for example, copyright might cover software, data sheets or graphic material; industrial design protection may cover packaging or the configuration of apparatus or diagnostic kits; and trade mark rights may need to be considered (see the case of Bollgard™ and Ingard™ in *Module Ten* for an example of this).

And of course clearing up freedom to operate from the point of view of IP rights does not clear the way to develop and commercialise a new technology. There may be a range of government

regulations, ethical standards, industry guidelines and cultural issues to comply with, quite apart from IP rights: for instance, in relation to the environment, health, ethical research and prior informed consent of those who have contributed biological materials or related traditional knowledge to the research.

Freedom to operate in different markets

Patent rights are territorial. This means that they operate only in the country in which they are granted. Freedom to operate in a particular country depends on whether patent rights are granted in that country. Many patents are registered in a reasonably small number of countries only – the

For example, imagine that you do a search on patent databases, and find out that there is a US patent on the technology you need to use in order to market your patented invention is already patented in the US but is not patented in any of the other countries in which you want to market you invention. In this example you would not need permission to practise your invention in any of the countries you checked except the US. However if you wanted to manufacture your invention in a country where there is no other patent on the technology and then import your invention to the United States, you would need permission from the patent owner in the US. If you do not, then you risk infringing the US patent owner's rights. Conversely if the US owner wanted to export the technology to a country where you have protection, they would need to seek your permission to do so.

What options are there for dealing with existing patent rights?

If you find that someone else has a patent for technology that you need to develop and market your invention you have several options:

- Firstly, if the other party's technology is very valuable to your invention you could seek a licence to use their technology and pay the owner for its use.
- Alternatively you could also cross-licence your technology to the owner in exchange for permission to use their technology or even negotiate a joint venture.
- If the technology is not that important to you, you could 'invent around' it so that you do not need permission to use it – in other words, find an alternative route to the same goal.
- You could develop a strategic research and commercial alliance elsewhere with other research and commercial partners who can provide a suitable technological and legal pathway to the same goal.
- If the patent holder has not made the technology available to the public on reasonable terms, then there is a possibility of gaining a compulsory licence to apply that technology. National laws differ on this point, and you would need to get specific legal advice. Compulsory licences can also be available in some cases when an earlier patented technology is required to implement a subsequent patented technology. In practice, the very possibility of a compulsory license might induce the other patent holder to grant you a licence on normal commercial terms, without going through the formal process of applying for a compulsory license.
- Finally, you might seek to oppose or invalidate the patent right. For instance, you may be aware of research in your field that was published prior to the patent right and which seems to anticipate the invention as claimed in the patent, or at least make it appear obvious.

It is always a good idea to get advice from a patent attorney or commercial adviser before you decide what to do if someone else has already patented technology that you need to use. This may be an issue that needs to be tackled very early on in planning the research program: if there is no real possibility of sufficient freedom to operate, the research program may be of little value and

may need to be redirected or even suspended. *Module Ten* contains a practical case study on freedom to operate, which gives you an opportunity to work on these issues in a practical context.

8.9 Negotiating Agreements

Ensuring your freedom to operate is another scenario in which you may have to negotiate an agreement – in this case, to reach an agreement to 'license in' the technology you need from the person, organization or company that holds IP rights over the technology.

Both *Module Eight: Researching and Intellectual Property Rights* and *Module Nine: Licensing and Enforcing Intellectual Property Rights* consider various other situations in which the IP system is used as a practical mechanism for researchers. Both modules consider the strategic use of licenses and other agreements as practical tools for deriving the benefits of the IP system. In many cases, the value of the system is derived less from the IP rights as such, than from the legal arrangements that are negotiated to put them into effect. Practical management of IP rights involves the effective use of legal documents which are intended to express in a structured and binding way different forms of agreement between partners. These agreements cover different ways of contributing to the research and development project (financial support, contribution of know-how and existing IP rights, logistical support, management, direction and research effort), different ways of conducting research activities (collaboration, by contracted tasks), different ways of assessing progress and deciding future directions (milestones, passage of time), and different ways of distributing risks, benefits and ownership of the results of the research.

Accordingly, during the course of a research and development (R&D) program, you or your institution will probably need at some stage to conclude a formal legal agreement with research partners, commercial backers or sponsoring agencies (such as government funding programs). So your practical awareness of the IP system needs to be supplemented by an understanding of the process of negotiating agreements, contracts and licenses.

There are many different potential arrangements for cooperation, and many different ways of expressing these arrangements in the form of legal agreements. Often, in practice, the nature of the relationship is predetermined by the use of existing model agreements or precedents, although this may not accurately represent the ideal arrangement for the two parties entering into the joint undertaking which the agreement is intended to promote. It is advisable, wherever possible, to think first about the nature of the practical arrangement you want to enter into, and then to think about how that arrangement should be expressed in legal terms, rather than limiting the cooperative mechanism to a pre-existing legal precedent.

In any case, the interpretation and legal effect of legal agreements can be a complex legal matter, varying considerably between different countries (and between jurisdictions within countries), so you should normally seek expert legal advice before entering into any legal agreement, even if it is a 'model' or 'precedent.' This advice needs to cover a range of issues. For instance, you should check whether the agreement really will achieve what you want it to and what you believe it does; you may need to check whether the rights and obligations you are entering into are reasonable, fair and legal; and you may need to check whether the other party is really has the legal, financial and technological capacity to enter into the undertakings it is assuming.

There is a range of legal agreements you may encounter in research and development of biotechnology, and the various categories overlap considerably, but they can be generally categorised as one of the following.

- ***Confidentiality or non-disclosure agreements***
  - Such agreements are used, for instance, when gaining financial support or bringing in potential collaborators for a new technology, before it has been patented, or in exploiting trade secrets. The agreement can limit the use to which the protected information can be put – for instance, it can be limited to evaluation purposes only, rather than other commercial or industrial uses. This provides legal certainty that the protected subject matter is not misused by commercial partners, and that disclosure of the invention in confidence is not considered the kind of 'publication' which can invalidate a later patent application. Signing a confidentiality agreement can create problems for companies who are working in the same field (for instance, the fact that they have independently come up with the same idea won't be evident until after they have already signed the confidentiality agreement and potentially constrained their future options for no benefit).

- ***Research-related agreements***
  - Such agreements can be used in establishing a research program, setting out the terms on which the partners provide financial support, undertake research collaboration or share technology, and the terms on which the benefits and ownership of the research outcomes are enjoyed by the research partners. They may cover the contribution of existing IP-protected technology ('base IP' or 'background IP') – for instance, one research partner might license the use of its IP for use in the project, subject to a financial or other contribution on the part of the other parties to the agreement.
  - Research-related agreements can include a research contract (see below), in which the researcher is paid to undertake a specific commissioned research task, and has no further rights or interests in the research outcomes, or other forms of research agreement in which the researcher has a more substantial interest.
  - A research and development agreement may be used when a research institute has identified a specific research direction, and needs financial backing to develop it. The agreement determines the conditions on which a funding organization (such as a public funding body, an investment company, or a commercial or industrial enterprise) provides financial support. Typically, the research institute may retain ownership of intellectual property rights, granting exclusive rights to the funding organization; or the rights may be held by the funding organization which grants the research institute exclusive rights.

A collaborative research and development agreement

- This kind of agreement is increasingly common in biotechnology research. A Collaborative R&D Agreement is struck when several parties agree to work together on the same research program. The parties come together because they share a common goal and need one another's resources or expertise to achieve that goal. They may also need to share some of the risks in the research and development rather than take on all the risks on their own. The parties agree to contribute various resources (which may be existing intellectual property, research facilities, skilled personnel, funding), in collective pursuit of a shared research and development objective.
- The management structure established to oversee such an agreement is important to its successful implementation, and if the research and development is aiming at a commercial product, it is important to ensure that the management structure has a wide range of expertise, not just the necessary technical or scientific knowledge. Key individuals, such as project leaders or leading researchers, may need to have their roles specifically defined, even though the agreement is strictly an agreement between several institutions.

- The collaborative R&D agreement will normally specify clearly the field of research, and establish clear goals or milestones – the milestones can also serve as specific decision points for planning future joint research or the commitment of additional resources, depending on the research outcomes at that stage and the external environment (such as commercial opportunities, the emergence of competing technologies, freedom to operate issues, and so on.) The agreement will also specify how long it runs for – whether this is a particular date or duration, or whether this is linked to certain milestones or achievements. It might contain provisions for either party to give notice of termination of the agreement.
- Ownership of IPRs on R&D outcomes may be shared according to agreed proportions, based for instance on respective inputs. The agreement might already make provision for commercialisation of research results (see *Module Nine*), or this could be separately negotiated (for instance, the parties could bid for licenses to commercialise the research outcomes, or a separate commercial or industrial partner could be brought in once the research outcomes were proven.)

- ***Material transfer agreements and information transfer agreements***
  - Used in establishing the terms on which materials (such as biological samples, cell lines, vectors, microorganisms etc.) or information (such as know-how or traditional knowledge) are provided, generally limiting the further use of the transferred materials or information, or providing for sharing of benefits resulting from any further use (e.g. a share of royalties on any commercial application of biological resources)

- ***Licensing agreements***
  - Used in 'licensing in' technologies that you need (e.g. paying a royalty to make use of a particular genetic engineering procedure), or in 'licensing out' technologies you have developed (e.g. receiving royalties for the use of transformation vectors you have developed). Many projects will require both forms of licensing at some stage. Your dealings with commercial or research partners might entail the transfer of technology licenses in both directions – a cross licence – in which each party to the agreement agrees to make some of its technology available to the other party, a kind of exchange of access or technology pooling.

- ***Commercialisation agreements***
  - Used when you need a commercial partner to bring a new technology to the marketplace, and deals with such issues as ownership, maintenance and enforcement of IP rights, payment for regulatory approval and marketing, and warranties as to the validity of the IP rights

- ***Sale or other transfer ('assignment') of intellectual property rights to others***
  - Used when you wish to sell the IP right to another party – and may include a provision allowing the developing of the technology to continue to use it (this would not automatically be the case)

- ***Research contracts***
  - This normally entails one party hiring another to undertake research and development as a contractor. The party providing the funding typically has a specific research proposal in mind, but lacks the specific research skills or technical capacity required to put it into effect. The researcher is therefore contracted to undertake the research on the funding

party's behalf. Since the funds pay directly for the research to be conducted, the funding party typically assumes ownership of any intellectual property rights on the contracted R&D, but the exact agreement as to ownership of IPRs needs to be spelt out clearly in the agreement, as the law might otherwise leave ownership of the rights in the hands of the contracted researcher.

- ***Employment and consultancy contracts***
  - The patent and employment laws of many countries provide that the employer and employee have certain rights over technology produced by the employee; but this situation can be less clear in cases where technology is developed fully or partially by an external contractor, or a research student, or employees whose duties lie in different areas. Specific contracts may be needed to clarify questions of ownership of intellectual property rights. For instance, in the absence of such a contract, an outside consultant retained to right a report could keep ownership of copyright in that report.
  - Employees, students, contractors and others may need to enter into specific confidentiality agreements as well. This can provide assurance to research managers and other partners that these individuals will be specifically obliged to treat sensitive information in confidence.

There is a wide range of options within each of these general categories of legal agreement, and whether you achieve the benefits you are expecting depends on whether you can negotiate effectively and with all the information and legal advice you need. It is an adage of licensing negotiations that 'you don't get the deal you deserve, you get the deal you negotiate.'

How should I negotiate agreements?

It is rare that a researcher in the biotechnology field can conclude a full research project without some form of external involvement and resources. The resources may be financial, or expertise, or access to technologies or biological materials you need. So it is likely that, at some stage of your research – perhaps even from its very beginning – you might find that you have to negotiate agreements covering your research. This may be a research contract that sets up a two-way relationship between you and commercial partners, between you and a funding agency, such as a charitable foundation or a government funding body, or between you and a collaborating research institute. This kind of contractual relationship defines, articulates and creates obligations for both parties, and sets out how the obligations are to be monitored, interpreted and – if necessary – enforced, and how disputes are settled.

Of key importance is for you to decide if you can have a beneficial relationship with the other partner. This may involve careful consideration of what your research goals are, and how to meet the overall objectives of your research institute, faculty or commercial enterprise. It also entails assessing carefully what resources you will need, so that you can determine who the right partner is. You may also need to consider to what extent you are prepared to compromise your objectives for the sake of reaching an agreement with a potential partner – whether it involves meeting funding guidelines for a public sector body, or whether it involves fitting in with the commercial strategy of a commercial partner.

If you decide to reach an agreement with a commercial partner to support your research, you need to make sure that you and the potential partner are going in the same research direction and have the same purpose. You need to make sure that you agree on the pace of the research and development work including the length of the relationship. Given that some contractual relationships can last for years, it is important that you build respectful and trusting personal relationships between you and your potential contract partners.

When you are negotiating with commercial partners you should focus on the benefits of the technology to their business. Essentially you have to convince them that it is in their interest to fund your research.

You should be confident of the outcomes of your research. While being confident you also need to be realistic about your outcomes. That is, don't make unrealistic and extravagant claims on what your research will do, and don't dwell on its pure scientific merits. At the same time, don't undersell yourself. This can be a very delicate line to tread, but with careful planning and inclusion of IP management strategies from the beginning, you are in a better position to make a realistic assessment of your work.

It is a good idea to make a prototype of your invention, or at least provide convincing evidence that your invention will work in practice. Alternatively, you should at least be able to demonstrate your invention to commercial partners. This will help commercial partners to understand your idea and help them to decide to provide funding for your invention.

If you are describing or demonstrating your invention to potential commercial partners before you have applied for a patent, you must get them to sign a confidentiality agreement. You also need to stop short of gaining commercial benefits from your invention before you file the patent application. Once you have filed your patent application, you have more room to move, although you may choose to keep your invention confidential until the patent application is published (normally 18 months after the earliest filing date) – this gives you the option of withdrawing your patent application in the event that your research direction changes or your overall strategy changes.

You will also need to tighten your timeframes for your project and improve your approach to accountability. This means that you will need to apply project management tools to both your research by identifying key milestones, and maintain financial accountability and responsibility.

Also, it is usually better to deliver a part-solution sooner to commercial partners, rather than a complete solution later. Your commercial partners will appreciate a part-solution sooner as it will give them confidence in your ability to deliver a product in a reasonable timeframe that will make money for them. A promising part-solution may also help in getting the funds and resources you need to take the research through to a successful solution to the problem you are working on.

Talk in commercial terms to your commercial partners, and accept that their priorities may be different to yours – they normally cannot afford to take a purely scientific or technological interest in your research. They are likely to be responsible for investment decisions involving other peoples' funds, and need to be able to justify their investment in your research from a commercial point of view. Commercial issues include:

- the amount of time it will take to get your invention to the market – this will need to fit in with the investment strategy of your commercial backers;
- the extent to which your invention is proven, and the amount of further work;
- the benefits of your invention to the end user, and the degree to which it fills a gap in the market and will be attractive to the potential market;
- the competitive advantage it would give your commercial partner, and the strategic fit of this technology in relation to their overall commercial operations; and
- the potential return on the investment to be made by your commercial partners.

Think about what would be needed to prove your technology's commercial value. Look at the technology in its commercial and social context, and consider it against competing technologies, your freedom to operate, and potential regulatory issues (environmental, ethical, consumer protection). Commercial partners are of course very focussed on time and money. More money this year may mean a bonus to them. If they invest in your invention and lose money it may mean they lose their job. Also, the more time it takes, and especially if you've underestimated the time

the development of your research will take, this adds costs and reduces potential return and commercial viability of your invention.

The development of a negotiation strategy is a team effort. It requires you, the scientific people, to work with your legal and commercial advisers. Your aim is to negotiate a win-win situation for your research organisation and the company investing in your research. Make sure that you and your research organisation receive a fair and reasonable deal. Be careful about deals that involve assigning your rights – it can be very hard to put an accurate value on IP rights, especially at an early stage of the technology. Even if you decide to assign part or all of your IP rights – assuming that their full value is recognised – consider your possible interest in maintaining access to your technology, and your interest in controlling further, downstream applications of your research outcomes.

RESEARCH AGREEMENTS

What should a research agreement include?

Ideally, a research agreement should:

- set out what you are going to do
- set out how much you will be paid, and when
- provide a mechanism to enable the program to be changed if necessary
- ensure your rights to publish your research
- protect confidential information
- set out what happens to the research results and intellectual property, and
- ensure that you don't get sued if the research work doesn't work, or something goes wrong.

Set out the research program and milestones for payment

A research agreement should set out the research program, that is, details of your research project. Also, the research agreement should say how you will be paid for your work. It is a good idea to provide in a research agreement that you will get paid in stages, over the term of the project. The agreement can list a series of recognisable milestones in the development of your research. These milestones can trigger reports to your commercial partners and payment to you.

Another way to stage payments is to be paid on a regular basis, e.g. quarterly, or some other period of time agreed by you and your commercial partner. In any case, you should normally seek some form of payments in advance of completion of your project.

Set out a mechanism for changing the project

It is very important for a research agreement to set out how the project can be changed. You might agree to deliver a certain kind of research but later find out that what you promised needs to be changed in light of further research and experimentation.

Many research agreements set up a Management Committee to be responsible for deciding how the research project can be changed. The membership of such a Management Committee should include representatives of both your research organisation and the commercial partner.

It is preferable for a Management Committee to make decisions by consensus, that is, by the agreement of all parties. Consensus will not always be possible, so the research agreement should state who has the final say about changes to the research project in the original contract.

The Management Committee must make sure that all changes to the original research project are documented fully.

The agreement should also cater for the entry of new parties, and the replacement of existing parties. Certain research personnel might be considered so important to the research that they are individually identified in the research agreement.

Ensure protection of confidential information and publication rights

Your commercial partners will want to protect confidential information as a way to make their investment in your research more valuable. You will probably want to publish your research results as soon as you can. The research agreement needs to say how these competing interests will be worked out.

The research agreement will not allow publication of your research to jeopardise IP rights. As discussed above and in more detail in *Module Two: Biotechnology and Intellectual Property*, you need to be very careful about when you publish your research results. Usually, if you publish your research results before you apply for a patent you will not be able to get a valid or enforceable patent. Your commercial partners will not want this to happen - and neither should you - as a patent can be a very valuable commercial asset for you.

The research agreement should provide for when research results can be published. This is a matter of timing. You should never give up your rights to publish your research results. You need to ensure that your publication rights are balanced against the need to keep your results confidential until you have applied for a patent.

Set out who owns research results and IP rights

A research agreement should provide a mechanism for seeking protection of patentable inventions and other intellectual property. It should be very clear on who owns the IP on outcomes from the research, who has access to this IP and on what terms, and who is responsible for financing the cost of obtaining and maintaining patents and other IP rights, including international protection, as well as obligations for monitoring and enforcing IPRs. You should, as a rule, aim to keep ownership or at least some control of your research outputs (although if you are an employee you will not normally be able to do this). For example, the contract could provide for you to file for the patent, prosecute it and maintain it, with your commercial partner having an exclusive license for a fixed term to market and seek a return on their investment in your invention. There can be benefits for both you and your commercial partners if you keep ownership of your research results and the IP rights over your research.

For the researcher, ownership has potential benefits. It allows for

- control over academic publications and subsequent use of the technology
- continuing access to the IP for further research and commercialization of the technology
- an opportunity to cancel a license if the company does not perform in marketing or applying the technology
- potential licensing of other applications of the technology to other commercial partners
- continuing contact and more opportunities for further research
- you keep ownership of IP if company goes bankrupt (the licence would be automatically finished if the company went bankrupt)

Whether you maintain ownership of IP may depend partly on your continuing interest in the technology and the research outcomes, partly on your capacity to take the financial liability and administrative burden of obtaining, maintaining and defending patent rights, and partly on your

negotiating skills. If you do decide to keep ownership of patents and other IP, it still might be possible to negotiate a research agreement that requires your commercial partner to help finance and support the obtaining and enforcement of IPRs – this would be so if you were granting an exclusive or sole licence to your partner (see *Module Nine: Licensing and Enforcing IPRs*). Depending on their interests, commercial partners might be prepared to accept your continuing ownership of IP rights even if they are making a substantial investment in your research. They may be able to obtain exclusive licensed rights that may be, for them, operationally the same as owning the IP right itself. They may see your continued ownership of the IP rights as a sign of your commitment to making the technology work, and to defending IP rights against infringement. They may also see it as a means of negotiating access to additional technologies being developed by your institution or university.

On the other hand, if partners are being asked to finance much of the research and assume considerable risk at the same time, they may find it difficult to justify this without the confidence and influence that flows from ownership or part-ownership of the ensuing rights. Negotiating some balance of all legitimate claims to ownership of IP rights is a crucial element in concluding research agreements, and generally needs to be tackled from the outset, as it can be very difficult and costly to deal with these issues later in the research program. Ownership of IP rights is not an end in itself, and if there are other ways of achieving your objectives (including longer-term objectives), then there may be room for flexibility in negotiations.

Joint ownership of research results and intellectual property rights is a legal possibility, although it can lead to practical problems. It can mean that neither party has complete control – for instance, your commercial partner may be able to use your research without paying for it and you may be constrained from licensing your research without their consent. There is an exception to these rules for joint ownership in the US. In the US both parties to a joint ownership agreement can use and licence their intellectual property rights independently of each other. However your patent attorney or commercial adviser should be able to correctly advise you on the best strategy to adopt.

Remember that a company's access to your research results will be an important issue for them. A company will not pay for something that you own if they might be stopped from using it. However, the needs of the company can be met without you giving them ownership of your research results and the intellectual property in them.

Access can be provided by several different mechanisms. These mechanisms can provide access at a later date. You can also give the company a "right of first refusal". This means that the company must always first be offered a licence on identical terms to those offered to any third party. A research agreement can also provide for a "lockout" clause. A lockout clause means that you will not sign a licence with any other party for an agreed time.

Provide you with protection against being sued

Do not sign a research agreement yourself - or at least not without advice! Research contracts should only be signed by an authorised representative of your university or research organisation. Individual researchers usually should not sign research contracts because if they do they will be personally legally liable if anything goes wrong. Be careful with research contracts. Make sure you do not get sued!

The contract should not provide any warranties that you can do the research project at all or in the time stated, that it will work, that it will meet expectations or that it will be of value. The contract should provide you with a release, which is a clause that says the company, will not sue you. Also, the research agreement should provide an indemnity clause. An indemnity clause provides that if someone sues you the company will pay for any damages. This is obviously important because if your commercial relationship ends you do not want to be bankrupted. You will need to get advice from your research institution, legal or commercial adviser before arranging for the signing of a research contract.

Checklist: the main clauses in a research agreement

- Definitions
- Research Program & Milestones
- Payments
- Extensions
- Management Committee
- Reports
- Patents
- Other Intellectual Property
- Publication
- Confidential Information
- Relationship between Parties
- Exclusion of warranties
- Release and Indemnity
- Assignment
- Right to enter Licence Agreement
- Dispute Resolution and Termination

CONFIDENTIALITY AGREEMENTS

Confidentiality agreements (or non-disclosure agreements) are often used in research and development. They can, for example, be used:

- with employees to ensure that they are aware of their responsibilities not to disclose information that could prejudice future patent rights, and to clarify (and enforce, if necessary) their responsibilities;
- with visiting researchers, students and contractors to clarify their legal status and obligations;
- with research partners (such as collaborating institutions) to facilitate the flow of information and cooperation between institutions, and to find solutions to technical problems, again without prejudicing patent rights;
- with potential commercial partners or funding agencies, allowing them to have access to technology for the purposes of evaluation and testing, for instance, so that you can get financial and other support for your project without forgoing your right to secure a patent.

Confidentiality agreements are of fundamental importance – failing to conclude an effective confidentiality agreement could lead to the loss of patent rights altogether. It is also the usual mechanism for exploiting trade secrets or valuable undisclosed information. In many countries' law it is not absolutely necessary to have a written agreement for confidentiality obligations to apply – but a written agreement provides greater certainty, clarity and protection against legal challenges. For instance, there should be some form of written acknowledgement that the material to be disclosed is understood to be disclosed in confidence, and that the obligation to protect it as confidential information has been accepted. It is usually advisable to define more precisely the nature of the confidential information and the nature of the obligation to protect it.

While you may often see 'standard' or 'model' confidentiality agreements, it is advisable to adapt the specific agreement to the nature of the information involved, the context of its use, and the needs and interests of the parties to the agreement.

Some elements which may be included in confidentiality agreements are:

- A statement of the purpose of the agreement and the disclosure of the confidential information (for instance, clarifying that it is only being disclosed for evaluation purposes)

- Definitions of various terms, including technical terms and terms that determine the scope of the agreement (e.g. defining the scope of permitted disclosure of the confidential information, or defining subsidiary bodies or associated research centres that may be covered by the permitted disclosure)
- The nature of the information covered by the agreement (for instance, the agreement could relate to a specific process that is being licensed as confidential know-how, or it could relate to all research activities that are conducted within a joint research project)
- The nature of the protection required (this could include requirements on the physical protection of the information)
- The scope of permitted disclosure – who is authorized to get access to the information (for instance, it might only be to certain nominated staff, or could be limited to a particular lab or research unit), including the need to put in place confidentiality obligations that cover the relevant employees or contractors of the institution receiving the confidential information
- The scope of permitted use (for instance, the confidential information may be provided only for technical or commercial evaluation, or only for non-commercial research, or only for the development of a particular commercial product)
- Obligation to return the information in the tangible form it was provided in (for instance, documentation or biological material such as microorganisms) once the permitted access has completed
- Ownership and management of any further intellectual property rights that are created as a result of the access to the confidential information, such as in the evaluation or testing process,
- Limitations on the further disclosure or copying of the protected materials (for instance, it may place restrictions on photocopying or digitally scanning documents containing confidential information)
- Time limitations on the permitted use of the confidential information
- Mechanisms for negotiating the extension of the agreement, either in terms of the scope of permitted use or disclosure, or in terms of its duration in time
- Monitoring and reporting on the use of the confidential information
- Details of financial payment or other requirements in exchange for the disclosure of confidential information
- Provisions on liability – for instance, disclaiming liability for any damage caused by use of or reliance on the confidential information

MATERIAL TRANSFER AGREEMENTS

Material transfer agreements (MTAs) cover the transfer of actual biological materials, and are used in a range of contexts, including:

- for exchange of materials between research institutes,
- for access to public germplasm collections (or 'seed banks'), and
- for bioprospecting, such as when outside parties (researchers or commercial enterprises) seek access to genetic resources in their natural environment (for instance, plants, plant components, or microorganisms) that are owned or cared for by an access provider, or that are located on land that is owned or otherwise the responsibility of the access provider.

MTAs are used in the transfer of physical biological materials that are of use in research and development – for example, germplasm or other plant propagating material, microorganisms, cell lines, cell cultures, nucleotides, proteins, and specific tools of genetic engineering such as vectors, expression promoters and DNA probes. MTAs are often used when these biological materials are exchanged between laboratories, research institutions and private companies. MTAs are also increasingly used to govern the conditions for access to plant genetic resources held in public germplasm collections: for instance, if you wish in your research to use a particular variety of rice, you may need to sign an MTA to get access to seeds held by the International Rice Research Institute in the Philippines. The recently concluded FAO *International Treaty on Plant Genetic Resources for Food and Agriculture* (see *Module One*) proposes a standard MTA that would be used for all access to plant genetic resources under the international system.

MTAs are also increasingly being used to deal with the relationship between researchers and custodians of biological or genetic resources in their natural environment, such as Indigenous and local communities, or government agencies responsible for management of public land, such as nature reserves. So MTAs may provide the conditions for access to and use of genetic resources that are found in a natural or traditional agricultural environment – for instance, when bioprospectors are seeking samples of plant material that may be of research or industrial interest. In keeping with the principles of the *Convention on Biological Diversity* ('CBD' – see *Module One*), these MTAs may be one aspect of guaranteeing that genetic resources are obtained with the prior informed consent of the community providing access to the resources, and are then used and exploited in a way that ensures an appropriate sharing of the benefits. In addition, MTAs in these contexts can also recognize traditional knowledge associated with the genetic resources (for instance, knowledge about cultivating, harvesting or processing plants, or therapeutic or other beneficial applications of plant material), and ensure that there are agreed benefits (financial or otherwise) in exchange for access to the traditional knowledge. They may also protect against certain unacceptable or inappropriate forms of usage of the genetic resources and the associated traditional knowledge. Traditional knowledge may also be protected by a confidentiality agreement, or by a distinct information transfer agreement.

MTAs do not cover IP rights directly, but instead reflect the fact that the person giving access to the biological material has control over it as physical property. They say, in effect, that in return for gaining access to the biological material itself, in its physical form, you will agree to comply with certain conditions (which may include payment or restrictions on what you do with the material). So the material transfer agreement establishes the basis on which this kind of useful biological material is shared. MTAs may involve an up-front payment or fee for the transfer of the biological materials, but they are can also involve arrangements for the ownership, control or use of developments resulting from the materials – so called 'reach through' provisions.

For instance, access to biological material may be provided, free of charge or subject to payment, in exchange for an undertaking that the material will only be used in a limited way. You might gain access to biological material for use in your research, subject to the condition that it may only be used for non-commercial research, that it may not be shared further without permission, that it may only be used in line with certain ethical guidelines, or that any IP rights or commercial benefits flowing from your use of the material should be shared in a particular way with the provider of the material. There may be conditions concerning liabilities for the use of the biological materials. A material transfer agreement articulates and clarifies this kind of condition on access to biological materials.

An MTA can include genetic resources that are covered by the Convention on Biological Diversity, particularly when the genetic resources are in their natural or traditional surroundings (either in the wild or cultivated by traditional communities). In this case, it will be important to include benefit-sharing arrangements and to ensure that any requirements for prior informed consent are complied with.

The MTA might clarify that legal title to (or ownership of) the biological materials remains with the provider – in other words, clarifying that the recipient is gaining access to the materials for the defined use, but that this does not amount to actual ownership of the materials – there may be an obligation to return or destroy the materials after the permitted use. It could specify that only particular defined individuals can use the material, or other personnel under the immediate control of a defined individual (for instance, the team leader of a research project). Apart from questions of IP rights, the MTA could specify also that the source of the materials be acknowledged in any publication of the results of any research using the materials. It could also require the recipient to report on all research results relating from the permitted use of the materials.

Signing confidentiality agreements and MTAs

Be careful when you are asked to sign one of these agreements, whether you are granting access to confidential information or biological materials, or whether you are gaining access. You need to make sure that the agreement benefits you and does not expose you to legal liability, do not unfairly restrict your research work, and is not unfair in its sharing of benefits and recognition of pre-existing rights. Make sure any agreement is reasonable and benefits you and the other party. Often you will be asked to sign a 'standard agreement' – but you should not hesitate to seek clarification or to question provisions in the agreement that you think could cause problems, that you don't understand, or that look ambiguous. This is especially the case if the agreement is not in your own language, or if it might be interpreted in a foreign legal system. Such agreements can be more complicated or more obscure than they need to be, and they can include provisions which are simply irrelevant or inappropriate to the actual situation. As with any technology agreement, wherever possible you should first try to clarify what the best practical working relationship is with the other party, before trying to define it in detailed legal language – rather than starting with a complicated draft legal agreement and then trying to work out what working relationship you wish to have.

Seek advice from your research institution or from legal advisors if you are asked to sign a confidentiality or material transfer agreement. If your research institution supports and signs the agreement it can protect you from personal liability if anything goes wrong. The entity who holds the legal rights should be the party to a confidentiality or material transfer agreement. The party should be the entity that has the capacity to protect the intellectual property rights and who accepts liability. A confidentiality or material transfer agreement must be signed by an authorised signatory on behalf of that entity – this may be the head of department of a research institution or university.

One of the issues surrounding these agreements, particularly MTAs, is how to ensure that both parties to the agreement are in a position to understand fully the consequences of the agreement. In the case of bioprospecting MTAs, there is considerable concern that benefit sharing arrangements should be fair and realistic, and should give full credit to the traditional custodians of genetic resources and to traditional knowledge. The principle of 'prior informed consent' in the CBD may, in practice, involve a considerable process of dialogue and cultural sensitivity to ensure that both parties fully understand the implications of the agreement and are comfortable with it. A full discussion of this important issue is beyond the scope of this Handbook (visit www.biodiv.org for some resources), but it does highlight a general point – negotiating and concluding agreements covers a very wide range of contexts, from the routine use of standard MTAs for researchers wishing to use research tools provided by other institutions, to complex and sensitive negotiations over access to genetic resources.

In short, concluding an agreement can be more than just a technical legal process and can involve establishing mutual trust and understanding so that the agreement reflects a sustainable and equitable working relationship. Of course in some cases, such as standard MTAs for access to research tools, these more general considerations do not apply and signing the MTA can become a

routine matter. But even then you should weigh the seriousness of the obligations you are undertaking before entering into a legal agreement.

8.10 Summary of Module Eight

There are many ways that researchers can get more out of the intellectual property system. For example, researchers should:

- maintain confidentiality until patent rights are applied for
- understand the state of the art in their field of technology
- know what competitors are doing, and consider potential partnerships
- keep good records and laboratory notebooks
- know the value of the likely outcomes of any collaboration, and what you want from the relationship
- seek early advice on the best mechanisms and outcomes, and
- research the company before conducting commercial negotiations with them.

Good research contracts benefit both you and your commercial partner. They help you to get on with your research and make and market your technological invention. Your commercial partners will be happy with the return on their investment in your research.

How do I protect my intellectual property while I am researching ?

It is too late to think about intellectual property rights at the end of your project. You need to protect your intellectual property while you are still researching by following these steps:

- know which kinds of intellectual property rights can protect your research, for example, patents, plant breeders' rights, trade secrets and trade marks
- prepare a combined intellectual property and research and development strategy that includes, among other things, checking prior art to make sure that your research has not already been done, checking the rights of third parties, and protecting your intellectual property
- use confidentiality agreements and material transfer agreements wisely so that they benefit you and protect your rights to your research, and
- keep good laboratory notebooks using the guidelines set out in this Module to help you prove when you make your invention.

What does "freedom to operate" mean?

Biotechnology inventions usually build on existing technology. Therefore, before you market your patented invention you need to make sure that you have "freedom to operate". Freedom to operate means that you can market your invention without infringing the rights of third parties. To get freedom to operate you need to:

- identify the rights of any third parties in patents
- identify the rights of any third parties in plant breeders' rights
- check patent rights in each country that you want to market your invention in because patent rights are territorial, that is, they only apply in the country in which they are granted, and
- get advice from you commercial adviser or patent attorney about what to do if someone else has patented technology that you need to use to market your invention.

How do I negotiate a research contract with commercial partners?

Research contracts between you and commercial partners can fund your research and help you to manufacture and market your invention. Some hints to remember are:

- commercial partners are focused on time and money so you need to talk in commercial terms to them to convince them to invest in your research
- research contracts should set out what you are going to do, how you will be paid, how the agreement can be changed, your rights to publish your research, how IP will be protected, who owns the research and the IP, and what happens if things go wrong, and
- you should never sign a research agreement without advice from your legal or commercial adviser.

8.11 Group Exercises - Module Eight

Please discuss Module Eight with your fellow participants and prepare answers to the following questions.

Exercise 8.1 - strategy for intellectual property and research and development

My Hanh is researching how to improve the quality of rice grown in Vietnam. She also is researching how to use gene technology to make a new variety of rice that is resistant to pests. This is My Hanh's first big biotechnology research project and she wants to make sure that she does everything the right way. She has started to write her research and development strategy for her project. What should My Hanh include in her research and development strategy? Why?

Exercise 8.2 - establish the date of your invention

My Hanh knows that a Japanese research company is doing similar biotechnology research to her research to create a new variety of rice. She is worried that even if she invents the new variety first the Japanese researchers might say they invented it first. My Hanh knows that if she wants to apply for a patent in the US for her new variety of rice she has to be able to prove that she was the first to invent her new variety.

(i) What should My Hanh do while she is researching to help her to prove the date of her invention?

(ii) Who can help My Hanh with advice on the intellectual property issues relevant to her research?

Exercise 8.3 - negotiating research contracts

My Hanh works at the Institute for Biotechnology Research. Unfortunately the Institute has just told My Hanh that they have no more funding for her research. To keep doing her research at the Institute she needs to get funding from new sources. My Hanh wants to negotiate a research contract for more funds with AgbioEnterprise, a business specialising in biotechnology investments.

(i) What kind of hints would you give My Hanh to help her to negotiate better with AgbioEnterprise?

(ii) What things should be included in the research contract?

Exercise 8.4 - freedom to operate

My Hanh is a successful researcher. She negotiated a research contract with AgbioEnterprise who provided her with funds to continue her research. After many years of research she eventually invented a new variety of high quality rice that is resistant to pests. In cooperation with her commercial partner she also got a patent for her invention. She now wants to market her rice.

(i) My Hanh thinks that the patent gives her the right to market her invention. Is this right? What issues does My Hanh need to consider?

(ii) How does My Hanh make sure that she has freedom to operate in the field of patents to market her new invention?

(iii) My Hanh finds out that some technology she needs is already patented in Vietnam but not in Thailand. Does My Hanh have freedom to operate in Thailand? What can she do to get freedom to operate in Vietnam?

A further exercise on 'freedom to operate' is provided in *Module Ten.*

FOREIGN AFFAIRS AND TRADE

AUSTRALIA

AusAID the Australian Government's overseas aid program

Module Nine

Licensing and Enforcing Intellectual Property Rights

Intellectual Property and Biotechnology

A Training Manual

Contents: Module Nine

9.1 Objectives for Module Nine

By the end of this Module you should have an understanding of:

- some ways for you to exploit your intellectual property rights to get financial benefits from them, including:
  - licensing your intellectual property rights
  - selling your intellectual property rights (that is, assigning your rights)
  - setting up a joint venture with commercial partners
  - setting up your own company
- the roles of the right holder and legal authorities in enforcing intellectual property rights
- the options for enforcing your intellectual property rights, including:
  - civil remedies including injunctions and damages
  - criminal offences
  - border enforcement measures

9.2 Background to commercializing IP

The cost of protecting IPRs

This module considers some of the practical intellectual property issues that arise when bringing a new technology to the public. Let's say you have achieved a breakthrough in your research, and have applied for a patent – what do you do next? There are many patents that have never been successfully transformed into new products in the marketplace – what goes wrong in these cases? In some cases, it's because the technology was not practically feasible, or was superseded by newer technologies. In other cases, the inventor lacked the resources or skills to take the invention to the next step.

One constant factor in the development of new technologies has been the cost and difficulty of the process of putting new technologies on the market. The technical merit or scientific brilliance of an invention is only one aspect of actually bringing a new technology to the public in a useful practical form. This can be a costly and complex process. Normally, it is not possible without a range of different partnerships and relationships – as sources of funding, expertise and other resources. Intellectual property protection needs to be properly managed so that it facilitates this process, and doesn't itself become a burden.

The problems of getting worthwhile benefits from the patent system - even for the patent owner – are not new ones, as this quotation from 120 years ago makes clear:

> Patenting was unnecessarily and unwisely expensive, and the poor patentee was left almost without any aid or guidance – *English Daily News*, 25th September, 1883

Intellectual property rights recognize innovative and creative activities, and are intended to reward useful and valuable contributions to society. But they are not direct rewards in themselves. All they do is to create an opportunity for the inventor or creative person to seek rewards for their invention or returns from their investment in the research. A patent can be expensive to obtain, especially if it is applied for in many countries, and costs money to keep in force, as annual renewal fees are required in many countries. In addition, patents can be very expensive to enforce if it becomes necessary to go to court to prevent infringement. Patents recognise inventiveness, but they are neutral on the commercial value of the invention. Many patented inventions will prove to be technologically unsuccessful, or commercially unviable. In many other cases, patented inventions which could be very successful fail to be developed because the inventor lacks the capacity, resources or skills to develop the invention commercially.

Many patent systems are run on a 'cost recovery' basis – so that the fees charged to patent applicants are sufficient to cover the costs of administering the patent office, or even to create a surplus. The Patent Cooperation Treaty (PCT) system administered by the World Intellectual Property Organisation (see *Modules Two* and *Three*) returns a surplus from the fees charged to private applicants, and these resources are used in many ways, especially in providing technical support and assistance to developing countries. So society does not reward inventors directly for making a patented invention – instead, it requires the patentee to pay his or her way in getting a patent, and then leaves it to them to see whether they can make money in a commercial way from the patented invention.

Some governments do provide support for small and medium enterprises, for instance in charging lower patent fees. The international PCT system also has greatly reduced fees for individuals in countries with low average incomes. But generally speaking the cost of the patent system is borne by patent applicants. And to the official fees must be added the cost of patent attorneys' or patent

agents' professional services in conducting patent searches, in preparing and filing patent applications (which may include the services of attorneys in several countries), in considering examiners' reports and preparing responses to the examiner's objections (patent 'prosecution'), and in maintaining the patent (and possibly advising on enforcement). *Module Three* describes the processes involved in getting a patent.

All this adds up to make the patenting process a significant investment. Following are *very approximate* costs (in Australian dollars) and the timeframe for a patent process commencing in Australia and using the PCT process (including official fees and typical attorneys' or agents' charges):

First step	Drafting and filing a provisional patent application	$2,500
12 months later	Drafting a complete specification (with claims) and filing an international (PCT) application	$10,000
20 months later	Request for international preliminary examination under the PCT	$1,500
30 months later	Entering the national phase (filing national applications in each country of interest)	$30,000
From approx 35 – 90 months	Examination and prosecution in each country of interest	$40,000

On these moderate estimates of minimum costs, the total already rises to over $85,000 – and this just takes the patent applicant to the point of obtaining a patent. Once the patent is granted, annuities or renewal fees are payable, typically once a year, and these fees normally increase over the life of the patent. This could typically cost a further $10,000 each year for the life of the patent – generally, up to 20 years from the first filing date. Costs in major jurisdictions, like the US, Europe and Japan are likely to be even higher.

This is only a very general and conservative estimate, intended only as an illustration. The actual sums involved will vary greatly from this estimate, and will very likely be higher, particularly if you are seeking protection in a number of major economies. Much depends on the number of countries you seek patents in, and whether any difficulties are found in getting a patent (for example, complex objections by patent examiners requiring significant amendments to the patent and legal argument and representations, or when a competitor challenges or opposes the grant of the patent). It is obviously much cheaper to seek patent protection in only your home country, but then you would have to accept use being made freely of your invention potentially in every other country. The cost of going through the patenting process in a number of countries is typically beyond the resources of all but the largest companies and research establishments, and most enterprises and institutions require some kind of commercial partnership or financial support to gain, and to keep in force, the patent rights.

The case is similar for other intellectual property rights, like plant breeders' rights, trade marks, and industrial designs, although these normally cost less overall than patents. The applicant takes a risk and invests time and money in the process of obtaining an IP right. The hope is that the IP right will improve their capacity to develop a new product and gain the benefits from their research and innovation. But when the costs are unpredictable and potentially high, and the future benefits from the IP right are uncertain and may only be realized after a number of years, it can be difficult to work out whether it is worth making the investment. Unregistered rights, like trade secrets and

copyright, do not incur direct costs in the same way, but may involve investment in physical security, preparation of confidentiality agreements, and monitoring and enforcement costs.

In short, obtaining registered intellectual property rights can be expensive, and do not in themselves make you any returns for your investment. Patents can be costly liabilities to you, your business or your research institute, unless you can find a way to apply your invention commercially or can get other forms of financial support. This calls for a range of skills and experience quite apart from technological and scientific skills. Often the most difficult aspect of putting a new technology to work, and of making it available to the public, lies not in the patenting process, but in finding a suitable commercial vehicle to gain suitable returns from the invention, including through commercial use of the patent. Commercialising inventions can involve a great deal of commercial risk, which small companies and research institutes might not be able to accept and manage. Because of these considerations, in many cases institutions and companies choose not to commercialise their invention at all, but elect to sell ('assign') or license their rights to the invention to other companies for them to take the invention to the marketplace.

Because intellectual property rights can be so costly to obtain, to keep in force and to enforce, they should not be pursued for their own sake. Patenting your invention may be worthless, and in fact could waste resources, unless you have a commercial strategy in which your patenting program has a logical place. And this strategy will usually involve some form of partnership – this may be a bank or venture capitalist providing you with the funds you need, a company with access to technology or a product that is needed for the success of your invention, or a commercial enterprise with product development and marketing skills.

When you are weighing up whether to commercialise your invention yourself, or whether you should find commercial partners or another way of developing your invention, you should consider:

- Your overall objectives: are you looking just to fund further research, or to create a new industry particularly for the benefit of your own country, or to build up a capital asset, or simply to disseminate the fruits of your research as broadly as possible, with some control over the way the technology is used?

- Your financial position: can you accept the cost and financial risk of investing in patents and other IPRs, and other aspects of commercialisation; do you have the reserves to defend and enforce your IPRs, potentially in several countries; will financial constraints keep you out of some of the major potential markets for the invention?

- The skills and resources you have available: do you, or your organization, have the capacity to develop and implement a product development and marketing program for a new product? What are the focus and core expertise of your organization?

- Regulatory requirements for getting onto the market: do you have access to sufficient expertise and resources to undertake the kind of testing and approval processes that might be required for a new product, such as a new pharmaceutical, a new pesticide or a genetically modified crop? Can you deal with labelling and certification requirements in different countries? Are there joint venture or local participation obligations to enter some markets?

- Your options for overseas production or export: do you have the capacity to produce, export and market your invention in major foreign markets?

- The nature of the technology: the invention may require access to other IP-protected technologies or know-how for it to be produced; and particular manufacturing technologies might be required for it to be made in an economic manner, so that the product is competitively priced.

- The strength of the competition: does your product need to find a place in a crowded market with strong competition, requiring the backing and resources of a major company in the field?

- The range of possible uses for your invention: do you have the capacity to put it to work in all the areas it could be used, or do you need partnership with others to make sure your invention achieves its full potential?

9.3 Options for exploiting IP rights

The question of how to exploit hard-won patent rights involves a range of legal, commercial and strategic judgments. This applies whether your aim is to maximize the commercial return from the invention, or to promote the widespread use and application of your invention. Managing patent rights effectively can be just as important for public sector organizations which are concerned how to ensure that the benefits of their technology are fully realized. If a public sector or charitably funded organization does not retain some IP rights over the new technologies it produces, this can have the ironic result that they lose control over how the technology is developed and applied, because other private entities are free to develop and patent their own improvements on the invention.

There are various ways of exploiting your intellectual property rights; these generally involve balancing immediate financial interests, risks, resources, and longer-term strategic and technology management interests. It is comparatively rare, particularly for research institutions, to bear all the risk and financial cost of bringing a new technology to market. At some stage, research partners or commercial partners need to be brought in. (See for example the introduction to the Relaxin patenting exercise in *Module Six* for the experience of a research institute dealing with these issues.) The relationship with a partner will depend very much on

- What stage is the invention at? Is it an unproven research insight, or a research outcome that is proven in principle but not fully tested in practice, or is it a fully operational prototype that is close to a consumer product? How much more research and development is required, and what are the chances of its success?

- What amount of risk, future commitment and financial investment is expected from the partner? Is the partner funding continuing research, or just brought in to use the invention with their existing processes? Have IP rights been granted, and checked for their validity; or are they just at the application stage, with no guarantee that IP rights will actually be granted in the future?

If the commercial partner is bringing to the market a technology which is well developed, has already been technically proven, and has been granted patents in the key markets, the commercial partner is taking on comparatively little risk, and the terms of the agreement should reflect that. On the other hand, if the commercial partner is being asked to fund continuing ongoing exploratory research, the outcome and viability of which is uncertain, they would expect a higher degree of interest in the intellectual property rights and greater long-term rewards in exchange for taking on a greater level of risk.

If you are a researcher working as a full-time employee, then your employer would normally have the rights to any patent on an invention that you develop as part of your employment (you may be entitled to specific rewards or compensation, however, especially if the invention is notable and

meritorious). Under many national laws and under the policy of many companies and universities, the inventor can be entitled to either the IP rights or some benefits from their invention – whether you are a researcher, manager or employer, you should be clear on the legal entitlement of the inventor to IP rights in the research outcome. In some cases, for instance, graduate students may not be bound by employer-employee obligations. Some institutions may permit you to exploit your rights yourself by entering into a commercial joint venture arrangement or starting up your own company to manufacture and market your product.

You will need to make fundamental choices about the path you take to commercialise the invention. This will entail first working out

- your overall objectives for commercialising the technology – what do you ultimately want to achieve? What benefits do you want from your research?

- your level of confidence in the technical utility of your invention, its commercial viability and the strength and range of IP rights – do you want to bear the risks, or do you want another institution or company to carry some or all of the risk?

- the financial resources and kinds of expertise you will need – can you afford to develop a new

Depending on these factors, you can choose between a number of different ways of managing your IP rights to get the benefits from your research. These options typically include:

- licensing your rights (an IP right such as a patent can be licensed out to others – either partially or fully, exclusively or to several parties)

- assigning your rights (an IP right such as a patent can be assigned, or its ownership transferred, to another – this can be in exchange for a financial payment or for some other valuable consideration, such as shares in the company)

- entering into a joint venture arrangement (you can effectively pool your intellectual property rights and other resources with a partner, to form a joint venture to develop and exploit a new technology), and

- starting up your own company to exploit the technology (often called 'spinning off' a new company, or a 'start-up' - this one approach taken by research institutions and university faculties to create a suitable commercial vehicle for putting new technology to work, while keeping basic research separate from applied development and commercialisation).

The discussion of each of these options focuses on patents, but very similar considerations apply to other forms of IP, such as trade secrets (undisclosed or confidential information), plant variety rights, industrial designs, trade marks or copyright. In fact, a range of different IP rights can be bundled together, to be licensed or exploited as a single technology package, together with arrangements for technical cooperation, staff training and other elements of a broader relationship. If you have a comprehensive package of interlocking IP rights and associated know-how, this could be more attractive to commercial partners, in contrast to a single patent or other IP right.

Licensing and assigning your IP rights

One basic choice is whether you should actively exploit your IP rights yourself, or to keep your IP rights and license them to others to use, or sell or assign the rights to another person. You can, in principle, make different choices in different countries for exploiting IP rights for the same

underlying invention. If you are based in Malaysia, you could in theory decide to exploit your patent yourself in the East Asian region, grant a licence a Canadian company to use the invention in North America, and sell or assign the rights in Europe to a Danish company – whether or not this is the best approach in practice is a different matter, of course.

A licence is a grant of permission made by the patent owner to another to exercise any specified rights as agreed. Licensing is a good way for an owner to benefit from their work as they retain ownership of the patented invention while granting permission to others to use it and gaining benefits, such as financial royalties, from that use. However, it normally requires the owner of the invention to invest time and resources in monitoring the licensed use, and in maintaining and enforcing the underlying IP right.

The patent right normally includes the right to exclude others from making, using, selling or importing the patented product, and similar rights concerning patented processes. The license can therefore cover the use of the patented invention in many different ways.

For instance, licences can be exclusive or non-exclusive. If a patent owner grants a *non-exclusive* licence to Company A to make and sell their patented invention in Malaysia, the patent owner would still be able to also grant Company B another non-exclusive for the same rights and the same time period in Malaysia. In contrast, if a patent owner granted an *exclusive* licence to Company A to make and sell the invention in Malaysia, they would not be able to give a licence to anyone else in Malaysia while the licence with Company A remained in force.

Licenses are normally confined to a particular geographical area – typically, the jurisdiction in which particular IP rights have effect. You can grant different exclusive licences for different territories at the same time. For example, a patent owner can grant an exclusive licence to make and sell their patented invention in Malaysia for the term of the patent, and grant a separate exclusive licence to manufacture and sell their patented invention in India for the term of the patent.

Separate licences can be granted for different ways of using the same technology. For example, if an inventor creates a new form of pharmaceutical delivery, she could grant an exclusive licence to one company to use the technology for an arthritis drug, a separate exclusive licence to another company to use it for relief of cold symptoms, and a further exclusive licence to a third company to use it for veterinary pharmaceuticals.

A licence is merely the grant of permission to undertake some of the actions covered by intellectual property rights, and the patent holder retains ownership and control of the basic patent. An assignment of intellectual property rights is the sale of a patent right, or a share of the patent. It should be remembered that the person who makes an invention can be different to the person who owns the patent rights in that invention. If an inventor assigns their patent rights to someone else they no longer own those rights. Indeed, they can be in infringement of the patent right if they continue to use it.

Patent licences and assignments of patent rights do not have to cover all patent rights together. Licences are often limited to specific rights, territories and time periods. For example, a patent owner could exclusively licence only their importation right to a company for the territory of Indonesia for 12 months. If an inventor owns patents on the same invention in five different countries, they could assign (or sell) these patents to five different owners in each of those countries. Portions of a patent right can also be assigned – so that in order to finance your invention, you might choose to sell a half-share to a commercial partner.

If you assign your rights, you normally lose any possibility of further licensing or commercially exploiting your intellectual property rights. Therefore, the amount you charge for an assignment is usually considerably higher than the royalty fee you would charge for a patent licence. When assigning the rights, you might seek to negotiate a licence from the new owner to ensure that you can continue to use your invention. For instance, you might negotiate an arrangement that gives you licence to use the patented invention in the event that you come up with an improvement on your original invention and this falls within the scope of the assigned patent. Equally, the new owner of the assigned patent might want to get access to your subsequent improvements on the invention.

Joint venture agreements and start-up companies

Rather than simply exploit your IP rights by licensing or assignment, you might choose to set up a new legal mechanism to exploit your technology. Typically this can be a partnership expressed through a joint venture agreement or a new corporation, such as a start-up or spin-off company. These options require much more work on your part than licensing or assigning your intellectual property rights. This could be a desirable choice in cases where:

- you want to keep your institute's research activities separate from the development and commercialisation of technology, especially when your institute has a public interest focus or an educational role; or

- you need to attract financial support from those prepared to take a risk with an unproven technology ('angel investors' or 'venture capitalists'), and they will only take on a long-term risk if they can get a share of future profits of the technology.

In working out the right vehicle for your technology, you will normally need specific legal advice from a commercial lawyer, preferably one with experience in technology and commercialisation in your jurisdiction. The laws governing partnerships and companies differ considerably from one country to another, and this discussion is only intended to give a general flavour of the various options.

A joint venture agreement involves a formal, legally binding commitment between two or more partners to work together on a shared enterprise. It is normally created for a specific purpose (for example, to commercialise a specific new technology) and for a limited duration. For instance, you might sign a partnership agreement with a manufacturing company to develop and market a product based on your invention. Before entering into a joint venture agreement, you need to check out possible commercial partners and make sure that the objectives of your potential commercial partners are consistent with your objectives. In the joint venture agreement, the partners typically agree to share the benefits, as well as the risks and liabilities, in a specified way. But this kind of partnership isn't normally able in itself to enter legal commitments, or own IP in its own right, so that the partners remain directly legally responsible for any losses or other liabilities that the partnership's operations create. In other words, a partnership which is not a corporation, a company or a specific institution doesn't really separately exist as a legal entity.

By contrast, a company is a new legal entity (a 'legal person' recognised by the law as having its own legal identity) which can own and license IP and enter into legal commitments in its own right. A spin-off company is an independent company created from an existing legal body – for example, if a research institute decided to turn its licensing division or a particular laboratory into a separate company. A start-up company is a general term for a new company in its early stages of development. If a company is defined as a limited liability company, the partners or investors normally cannot lose more than their investment in the company (but officeholders in the company

might be personally responsible for their actions in the way they manage the company). This separate legal identity means that a start-up company can be a useful way of developing and commercialising a new technology based on original research, while keeping the main research effort of an institute focussed on broader scientific and public objectives, and insulated from the commercial risks and pressures of the commercialisation process. At the same time, the research institute can benefit from the commercialisation of its research, through receiving its share of the profits and growth in assets of the spin-off company, thus strengthening the institute's capacity to do scientific research.

The company is normally owned through shares (its 'equity'). These effectively represent a portion of the assets and entitlement to profits of the company. Investors can purchase shares in the company, which is one way of bringing in new financial resources to support the development of the technology – in exchange, the investors stand to benefit from the growth in the company's worth, as their shares proportionately rise in value, and to receive a portion of any profits produced by the company's operations, commensurate with the number of shares they own. If it is a public company, shares in the company can be bought and sold on the open stock market. An initial public offering is when the shares in a start up company are first made available to the public to purchase. A private company's shares, by contrast, are not traded on the open market (but can still be bought and sold).

The option of starting up your own company to manufacture and market your patented invention requires you to have business skills, marketing skills, management skills and substantial capital to draw on for factory premises, hiring staff and so on. But it also can offer a mechanism for attracting financial backing for research, development and marketing, which can improve access to the necessary resources and expertise.

Which model of commercialisation is best for you?

Each new technology and associated package of IP rights is potentially difference, and the mechanism you choose for commercialisation should take into account the particular features of the technology. One basic consideration is to what extent you, as originator of the technology, wish to be involved and to invest in the subsequent development of the technology. You will need to compare the advantages and disadvantages of each model of commercialisation. Generally speaking, the higher degree of risk and commitment of finance and resources you can invest, the higher the degree of control you can secure over exploitation of the technology invention, and the higher the financial return to your institution may be. This is illustrated in the table below, which compares four models of commercialisation using the criteria of risk, profit, management and control.

There are many possible variations on each of these general models, and in practice they can overlap. In deciding which model of commercialisation is best for you, it is always a good idea to seek commercial or legal advice.

Remember that IPRs alone do not guarantee you a financial return on your invention. You need to make good commercial decisions to benefit financially from your intellectual property rights. Properly managed, intellectual property rights should not be a burden but should yield a return from your hard work in creating an invention.

COMMERCIALISATION MECHANISMS				
Model	**Risk**	**Profit**	**Management**	**Control**
Assign	None	Very low ➞ medium	None	none
License	Low	Low ➞ medium	Low	Low ➞ medium
Joint venture	Low-medium	medium ➞ high	High	Medium
Start up	High	none ➞ very high	None ➞ high	According to equity

The following interview discusses the particular issues that need to be weighed by universities and public research institutes in relation to commercialising their IP, and the role of the Technology Licensing Office (TLO), a specific unit established in some universities to advise research staff on IP matters and to undertake management and licensing of university research. For more information about commercialising your research, you can also refer to *Module Ten: Case Studies on Commercialising Research*.

COMMENTARY ON COMMERCIALISING IP FROM RESEARCH

Following is the text of an *IP-Wire* interview with François Bourgeois, Chairman of the European Physical Society Technology Group and former Technology Transfer Coordinator at CERN.

IP-Wire: Historically, universities and publicly funded research institutes have placed great value on the open and free exchange of scientific and technological information. How has this been affected by the modern global economy, in which intellectual property rights (IPR), increasingly, play such an important role?

François Bourgeois: The two worlds of basic science and the modern global economy are dramatically different, in particular when it comes to measuring success. While the scientists' main goal is the search for long-term benefits for mankind, the global economy is primarily striving for wealth creation. However, both communities are living in highly competitive environments where "novelty" is a rewarding factor. For scientists, novelty is assessed through a system of peer reviews and publication in specialised journals. A code of honour and common sense determines who was first to make the discovery. For the global market the patent system establishes the date of first invention and the right to make, use or sell it for a limited period (20 years), in return for public disclosure of the technology. Some secrecy is associated with the filing of a patent. It is also true

that competition between scientists can incite them to keep confidential their progress towards the goals of their research.

Technology bridges the gap between these two groups of people and it is often intimately mixed with basic science and education. Technologists have in general a better literacy in IPR and they are more exposed to the free market economy. Since the middle of the 1970s, technologists and scientists have been increasingly expected to find part of their funding through contract research activities; hence they were given incentives to move towards a "patent or perish culture". Basic science and academia were not prepared for this dramatic change, which was seen as impairing the free exchange of knowledge they had enjoyed ever since universities were created. In addition, they saw the patent system as a tool to disclose trivial inventions such as "better mouse traps" or new types of barbed wires, and therefore an insufficiently rigorous medium to publish scientific work. If life sciences have now fully swallowed this change, it must be said that physical sciences are still somewhat reluctant to do so. In actual fact, I am convinced that the introduction of IPR policies in universities and publicly funded research institutes has little affected the open and free exchange of information in basic science. The proof of this can be found in the USA, where universities have long practiced proactive IPR policies without impairing communication with other academic and R&D institutes in the world.

On the other hand, competition in the search for private sources of funding has significantly diverted the scientific community from its basic mission. I am convinced that basic science should not be market-driven and that scientific policy makers should fund it adequately.

IP-Wire: Some people have suggested that the necessary secrecy involved in obtaining IPR protection impedes technological progress and innovation by keeping information hidden. What is your opinion on this?

François Bourgeois: It is often overlooked that the prime goal of the patent system is to foster the disclosure by publication of technologies that would have otherwise remained as trade secrets. Trade secrets can be kept for much longer than the few weeks to few months of secrecy associated with the filing of most patents. In any case, patents are published 18 months after the filing date and are thus publicly disclosed. It must be emphasized that patent information is not secret and patents describe technology in a standard format. At the time of the Internet web (WWW, invented at CERN), patent databases are major sources of structured scientific information. The argument of secrecy is put forward by those who refuse to adapt. In my opinion, the problem is not secrecy but rather the lack of IPR culture. It is a pity to see that some developments presented in topical conferences have been already patented, sometimes long ago.

Early internal disclosure of new technology to the supervisor (or the Technology Licensing Office) is highly recommended to limit the widespread feeling of "not being informed". A proactive IPR policy helps identify unused and often poorly documented technologies, which are bound to be lost when the person owning the "know-how" leaves the organisation. Early reporting will allow for the swift filing of a patent whenever justified.

IP-Wire: Could you briefly outline the phases generally involved in the transfer of technology developed by a publicly funded research institute from the 'idea' stage through to market exploitation?

François Bourgeois: Between 'idea' and the commercial product (or process), one can identify two intermediate stages: the demonstrator and the prototype. Technology transfer can take place at any of these stages but depending on the stage at which it occurs, the interactions with the receiving party and the returns can be very different. I shall therefore assume that the 'idea' has been identified as patentable and that it is likely to generate returns in terms of image or revenue.

This first stage involves a search for prior art and a preliminary market survey. This phase can take less than two weeks and the inventor, the TLO, a patent attorney or a technology broker can help. In my experience less than 50% of the ideas perceived in first instance as "very good" really merit patenting. The reasons are manifold: existence of prior art; the idea does not bring sufficient savings when compared to other established competing technologies; regulations limit the field of application, etc. This phase can take less than 2 weeks and, if positive, it results in a first filing in a national patent office. At this stage and unless there is room for other related patents, the inventor can publish his invention and openly pursue his developments.

It is then highly recommended to proceed with a thorough technology assessment and market analysis during the 12-month additional delay before international (and costly) extension to other countries. During this time frame, the inventor will develop a demonstrator and, if possible, a prototype. In parallel, the TLO (or a technology broker) will market the invention and identify potential customers. This joint effort will result in an assessment of the expected income and the wording of draft licence agreements with third parties. It may also lead to a joint venture or a start-up (with or without the inventor). If the expected income does not cover the patent costs (typically 6Keuros/year), the organisation will have to decide whether the transfer can be justified by the indirect returns associated with a strengthened image.

IP-Wire: What, usually, is the timeframe for such a process?

François Bourgeois: To summarize what I said before in this respect: 4-6 weeks are needed between the disclosure of the idea and the filing of the patent in a national patent office (the real period during which secrecy must be maintained); an additional 12-18 months permit a thorough technology assessment and market evaluation. Then, depending on the terms and conditions of the licensing agreement, 3-5 years are required to break even!

IP-Wire: What is the function of a Technology Liaison Office (TLO) within the technology transfer (TT) process, and how important is it for research institutes to establish one?

François Bourgeois: H. McKinnell, Chairman and CEO, Pfizer Inc. has said, "Technology transfer is people to people. You have to commit the people to make it work".

I cannot agree more with this statement. The inventor will be deeply involved in all technical dealings with the licensee and, unless the transfer is of mutual benefit, his supervisors will lose part of their human resources. A TT policy should plan for potential diversion of part of the organisation's staff away from the main programme.

The role of the TLO in a publicly funded organisation is that of a facilitator with a scientific background, literacy in IPR and licensing, providing help for the scientist, not a problem maker. It should be the focal point of contact for any individual who feels that he has a patentable idea. The TLO should be a lightweight unit and be on excellent terms with the hierarchy in the other units of the laboratory.

A TLO should exist whenever the organisation has an approved technology transfer policy. Without a TLO, TT will soon be 'à la carte' and IPR issues will be left to the initiative of the individuals. The direct consequence is that third parties will develop a poor opinion of TT from the organisation. The TLO should receive sufficient funding to pay for the help of patent attorneys and technology brokers. Such TLO offices seldom require more than a handful of motivated people. Good examples are the European Space Agency (6 full time equivalents) or Stanford University (25 or so).

IP-Wire: What are the pros and cons of dealing with TT in-house, as opposed to having an external organization manage it on an institute's behalf?

François Bourgeois: Sub-contracting TT activities is an excellent model because it clarifies the economics of TT for the organisation and prevents diverting staff from the basic mission of the laboratory. It remains that, in such a case, it is advisable to keep a small in-house TLO to act as a central point of contact and interface to the external structure.

Unfortunately, very few organisations can afford the fixed costs incurred by such an external structure and I am of the opinion that seeking assistance from patent attorneys and technology brokers on a case-by-case basis is a better alternative.

IP-Wire: Once a research organization has developed a new technology, what options are open for the exploitation of its IPR?

François Bourgeois: The options can be grouped under three headings: licensing, entrepreneurship and consultancy (knowledge-transfer, person to person). The latter is also part of the first two.

The option of entrepreneurship through start-ups or joint ventures provides the best returns as long as it has been adequately planned in the TT policy (stock options at a level permitted by the legal framework governing the organisation).

Licensing generates moderate revenues and requires a minimum of legal/commercial literacy on the part of the TLO staff. Using this model, it usually takes 3-5 years before a TLO breaks even.

Consultancy is a good option as long as it does not turn into 'work for others', in which case it results in a net loss of resources for the organisation. It has been shown that consultancy fees can easily cover patent expenditures and TLO staff costs, as well as compensating for the cost of the staff assigned to the consultancy actions.

IP-Wire: What are the key factors technology developers need to be aware of in order to optimally exploit their patents and copyrights?

François Bourgeois: The best advice I would give in this respect would be for the developer to have a thorough knowledge of the prior art and of the competing established technologies. Developers should never forget that however good their invention might be, the market and the customer will decide in the end.

Then, if they are young and prepared to team up with finance and marketing experts, they should consider entrepreneurship.

Last but not least: time to market is a key factor for success, therefore beware that in some cases "if you had time to patent your discovery, it is out of date".

9.4 Working with technology licenses

This section concentrates in particular on the details of a technology licensing. This is a practical aspect of IP management and use that affects many researchers, even those without a direct commercial interest.

A licence has two general functions – it is a legal document, a contract which creates legal obligations that apply to the parties that enter into it; but it also helps to define and shape a commercial relationship. The better these two functions are coordinated, the more likely it is that the agreement will be workable and mutually beneficial. On the other hand, what you put into a licence is often affected by other areas of law – contract law (for instance, determining what amounts to an enforceable contract), competition law (so that the license provisions don't amount to unfair competition), and intellectual property law (for instance, the national patent law might specify that certain abusive forms of license are invalid – such as a term in a license forbidding any challenge to the validity of the patent). So the mere fact that something is mentioned in a licence doesn't automatically make it an enforceable obligation – this is a question that can only be answered by a commercial lawyer with knowledge of your national law.

Generally speaking, you should ensure that you understand the licence and get independent advice on any complex legal terms that you can't understand. This will help ensure that you conclude licenses that make sense to you in terms of what you and what your partner are trying to achieve, and what you expect of each other.

In some cases, there will be very little flexibility in the licensing negotiations. If you are one of many people licensing in a particular technology from a major institution, the patent holder might have very little incentive to make special arrangements for you. On the other hand, you might have particular skills, expertise or other IP rights that can put you in an influential position in licence negotiations. If you are licensing your technology to others, you will be in a stronger position if you know your own technology well, have investigated the freedom to operate issues, have done research into alternative or competing technologies, and know well what your potential licensing partner needs.

When you are exploring possible licenses for your own technology, you should try to consider:

- Can your commercial partner make best use of the technology, including applying it to new or different areas, and development improvements and adaptations of it? Does your commercial partner have a track record in bringing new products to the market?

- Is it a major new technology, a key breakthrough with potentially broad application in a range of technological fields, or is it an improvement to existing technology with a limited or specialist scope of application?

- Is effective use of the technology is dependant on access to other technology, covered by other IP rights? If so, what is the pattern of ownership of that technology – who owns it, and in what countries?

- Are there strong IP rights, or is the IP position uncertain - have rights merely been applied for, or are have patents been granted on the invention? Is there a comprehensive package of IP rights? What is their geographical coverage? How much longer do their terms run for?

- Do you need immediate financial returns to recoup your research costs, are you prepared to wait for longer term but potentially higher returns, or do you need some mix of both?

- What is the likely commercial future of the product using the licensed technology – is it still experimental, has it been proven technically but not market-tested, or is it likely to be put on the market in the near future with demonstrated commercial potential?

- What is the nature of the IP protection – for instance, would trade secrets or confidential knowhow be vulnerable if it were disclosed to too many people or to several competitors?

- What level of investment will be needed by the commercial partner, apart from license fees and royalties – will they need to invest in getting regulatory approval or in developing new manufacturing processes?

The answers to these questions will influence fundamental licensing choices, such as whether to structure the license on exclusive terms or whether to adopt an open licensing strategy, and whether to seek up-front payments or to base the return on future royalties. Once you have a good general sense of what you would like, and what you could realistically expect, from a licence, you will be in a better position to think about specific terms for the licence.

A licence agreement should define what is being licensed, and what is not: it could set out the intellectual property rights that are being licensed and who retains ownership of the rights, including rights on improvements to the licensed technology. It also should be clear on whether the licence is exclusive or non-exclusive – the difference between these can be fundamental.

A licence agreement should set out how royalty payments will be calculated and when they will be paid. Before you enter into a licence agreement you will also need to decide who will be responsible for paying the costs of maintaining the patents or other IP rights for the duration of the licence. A licence agreement should define clear performance milestones and set target dates for them to be met. There should be provision for maintaining confidentiality where necessary, while still allowing you to publish your research.

Licensing agreements need to cover other issues such as insurance, and releases and indemnities. Dispute resolution and termination clauses are also important. If there is a dispute over the terms of the licence it is always a good idea for parties to have an agreed way of settling the dispute, such as mediation or arbitration, rather than having to resort to legal action in the first instance.

In summary, a technology licensing agreement will normally:

- name the intellectual property rights being licensed
- make it clear who retains ownership of the intellectual property rights
- state how the royalty rates will be worked out
- set out when royalties will be paid, including milestone payments
- set out which territory the licence applies to
- set out whether the licence is exclusive or non-exclusive
- set out whether the licensee can licence the intellectual property rights to others
- state who will pay the costs of maintaining the patent rights
- set out arrangements for dealing with improvements and new applications of the new technology
- set out how confidentiality issues will be dealt with and the rights of the inventor to publish their research

- provide for an insurance, release and indemnity clauses
- provide for dispute resolution and termination

Choosing a potential licensee can be very important, as you are relying on this commercial partner to deliver the benefits of your technology – not only the commercial benefits, but the benefits to society that might come from the full dissemination and widest possible use of your technology. The choice should not just be based on willingness to pay a higher royalty. A partner who has a convincing business plan and establishes a good working relationship with you is likely to be more valuable. If you are selecting a licensee, you may need to consider a host of factors, including:

- Does the company have experience and proven success in developing new technologies and bringing products to market?

- What kind of R&D and business plan does the company have? Are there realistic plans for developing and distributing the product based on your technology? Do these plans have well-defined milestones that could be built into a license agreement?

- Do you want to favour development of the technology in your own country? Is the company willing and able to invest locally in facilities for exploiting the technology?

- Are the resources, expertise and reputation of a large, established company needed, or are the flexibility and lower costs of a smaller, start-up company more appropriate for the technology?

- Are you planning to export your technology or otherwise develop overseas markets? Is your potential partner established overseas, or have experience in foreign markets?

- Is your commercial partner likely to be able to take up new applications and improvements on the technology that your research is working towards? Are they able to apply the technology in all the potential areas of use?

Due diligence

Of course, your commercial partner will need some reassurance about the quality of the offer you are making to them. If you are involved in licensing technology or seeking commercial support for your research you are likely to hear of 'due diligence.' When a future partner is considering whether or not to license technology, to buy a share of patent rights, or to support your research, they will need to satisfy themselves that it is a viable proposition. The process of assessing the viability, risk, potential liabilities and commercial prospects of a project is known as 'due diligence.' Indeed, if a potential partner seems not to be interested in this kind of issues, it may actually raise questions about their commitment to the project or the credibility of their business plan, particularly if the relationship assumes some degree of risk and investment on their part.

Generally, due diligence will involve assessing the overall commercial operations, cash flow, assets and liabilities of a business that is being purchased or otherwise financially supported. You would think twice about purchasing a business if you found that it was burdened with debts, or was about to be involved in difficult litigation, or if there were doubts about whether it really owned its assets. The same applies to a potential investment involving intellectual property. For instance, a potential commercial partner would not want to invest in patented technology only to find out that patent renewal fees have not been paid and the patent has lapsed, or to find out that the patent was being opposed by another company, or to find that there is prior art available that calls into question its validity. It may transpire that a student, a contractor or a visiting researcher could

actually be legally entitled to some or all of the patent rights. Even a serious level of uncertainty or doubt could be enough to deter a potential partner, especially if they have run into this kind of difficulty before.

Due diligence may also involve searching for information about the full range of IP rights that might impact on the relevant technology – for instance, to check whether you have later filed patent applications on improvements to the original patented technology, that may limit the value of their investment in the original technology. Other intellectual property rights – such as related trade mark or design registrations, or key trade secrets or copyright material (such as manuals or software) – may also need to be identified or located, as these may also affect the commercial partner's interests in the technology. For example, they may be unwilling to take out a licence for your patent without getting access to the software you have developed for a related process. They may want the right to use your trade mark in association with the patented technology.

So in a due diligence process, your commercial partner may undertake a range of checks and need various forms of information. These may include:

- checks on external records, such as patent registers and patent databases, including foreign patents;
- searches of patent databases for conflicting technology;
- independent advice from patent attorneys on issues such as patent ownership, patent validity and scope of patent claims;
- checks on employment contracts, confidentiality arrangements, and contracts with other parties that may interfere with the exercise of IP rights;
- details of the patent prosecution such as examiners' reports and other opinions;
- details of any legal challenges to the patent, and the way the proceedings were resolved;
- checks on laboratory notebooks in the event that the validity of US patents is of concern to the commercial partner (this also provides reassurance as to claims of ownership of the patent);
- surveys of the activity of competitors and owners of competing technology, and possibilities of conflict; and
- analysis of freedom to operate issues.

In preparing to licence your technology, you should consider in advance these kind of due diligence issues. If you can anticipate and provide comprehensive answers to these questions, you will be able more effectively to reassure your commercial partner, and you will be in a stronger negotiating position in negotiating licence terms. It should also speed up the licensing negotiations, and ultimately the commercialisation of your intellectual property.

DECODING LICENCES AND TECHNOLOGY AGREEMENTS

Licenses on IP are literally a part of everyday life, although we are not always aware of this. When you buy a book, a software package or a music CD, you may be buying a license for limited uses of copyright material – you normally don't get an unlimited licence that permits you to do whatever you like with the copyright material. This is unlike the case if you buy other objects – say a computer, a CD player, or a screwdriver – when the person selling the object can't normally restrict the way in which you use it. For example, when you buy a music CD, you are normally only paying for an entitlement to play the music in a private environment. You would need to get a separate license to make and sell copies of the CD, or to play the CD in a public restaurant, or to broadcast the CD on public radio. If you buy a software package, you might only be given a licence to use the software only on one computer, and to make only one copy of the disc for back-up purposes. You might need to get a separate licence to install the software on a network, or to make numerous copies of the software to distribute within your organisation.

Researchers in the biotechnology field increasingly find they have to read, understand, negotiate and enter into, licences covering the technology they are working with. While these are different in scope and subject matter to the kind of licence that comes with a word-processing package or music CD, the basic elements of licenses remain the same. The license defines certain limited uses of IP material, and sets out conditions on this use. This entitlement is normally given in exchange for some form of payment or other benefit. A licence may be free of charge, but could limit the way the licensed IP is used.

This section discusses the main elements of licensing agreements. But beware: this is only a general introduction to a complex area of law. If you ever get involved in serious licence negotiations, you should seek expert advice with experience in the national legal system (or systems) you are dealing with.

The parties to the licence:

The 'parties' to the licence are the entities (individual people, companies or institutions) that are bound by the licence as a legal contract. They normally sign (or 'execute') the licence to confirm in a legally clear-cut way that they agree to comply with its terms. The parties can be individual persons, but they are normally legal entities such as a research institution, a university or a company. It is important to ensure that the licence is signed in a way that is legally binding, and by a person authorized to sign for their institution. The institution itself has to have 'legal identity' under the relevant national law – it has to exist in a legal sense. A research team, a division within a research institution or a joint venture partnership is probably not able to sign a licence in its own right – either the individuals concerned have to sign the licence and become legally bound by it as individuals, or the licence has to be signed on behalf of the overall organization or company.

In some cases, the licence is not directly signed (think of the 'I Agree' block which you are often asked to click when installing a software package on a computer), and in the national law of many countries, contractual obligations can arise even without a formal signed document.

Following are some of the basic provisions you will find in many technology licenses.

Licensor and licensee:

The person granting the licence – the 'licensor' - typically holds rights to technology, biological material, IP rights, know-how, or other information. The person receiving the licence – the 'licensee' – is the party which is seeking to use or exploit that material.

The basic idea of the licence is that the person granting the licence (the 'licensor') is giving another person (the 'licensee') the right to do something that they could otherwise prevent them from doing, in exchange for some kind of benefit (this may be financial, but may be other forms of benefit). So the licensor might permit the licensee to use a technology that is covered by a patent – and if there was no license, the licensor could take legal action under the patent to prevent this use of the technology.

In effect, the legal purpose of the license is to guarantee the licensee that they can use the patented technology confident that there will be no legal challenge from the licensor on the basis of the patent right. Normally, the licensee will get other less specific non-legal benefits that flow from a cooperative relationship with the people who created the technology, including technical advice and know how.

Definition and scope:

The licence will normally define what its subject matter includes, and what the purpose of the licence is. For instance, it could define the subject matter as falling within the claims of a certain patent. The subject matter could be broader than that, however – it might involve access to related knowhow (including confidential information) that might assist the licensee in using the patented technology, and it might involve use of a related trade mark, industrial designs or copyright material.

The definition could define the subject matter in some detail as 'licensed rights' or a 'technology package,' or it might just refer to specific patents by number. If the technology is at an early stage – for instance, if patent applications are still in process, the definition might have to make clear that the scope includes any patents granted on the basis of those applications, or only those patents which relate to a specific use of the technology covered in the applications. It could also apply to any derivative patents, such as continuations of the original patent application.

If the licence includes unregistered intellectual rights, such as know-how or trade secrets, special care should be taken to define this so as to avoid future uncertainty and potential disputes. If the licence covers both patented technology and trade secrets (confidential know-how), it may be necessary to specify that what occurs in the event of the patent or patent application lapsing – does the licence still apply to the trade secret or know how?

Grant of licensed rights:

The license needs to define what rights under the defined intellectual property the licensor is granting to the licensee – for instance, the right to use a patented process to produce a certain product. The licence could specify an also define certain permitted usage of the licensed technology – for instance, the permitted usage may be limited to one industry sector only (e.g. the licensed use for a new chemical entity covered by a patent might be defined as only for agricultural use or only for human pharmaceutical use). It might limit the use to research or non-commercial use.

It might also clarify what rights are not being licensed – for instance, the patented technology, but not the associated trade mark. It might specifically reserve certain rights, such as the right to use patented improvements of the licensed technology.

Sole, exclusive or non-exclusive licences:

The choice taken among these options is very important. An exclusive licence means that the licensor agrees not to grant another licence to any other party, and agrees not to use the licensed rights (in other words, the licensor cannot become a competing user of the licensed technology). A sole licence means that the licensor grants a licence to only one licensee, the sole licensee, but the licensor retains the right to use the technology itself. Under a non-exclusive licence, the licensor grants the licensee a right to use the technology, but the licensor can still give the same rights to other licensees. The kind of license granted will depend on several factors, and will do much to influence the pattern of use, and the scale of royalties or other payments, made by the licensee.

The scope of exclusivity given to the licensee would normally be matched by stronger expectations of the licensee's diligence and active exploitation of the technology. After all, in many countries, the law can intervene and grant compulsory licenses to third parties if the patent is not adequately worked after three years. Exclusive licenses may be particularly important when the licensee is expected to make considerable investment in bringing the technology to the market – for instance, in undertaking the regulatory requirements for the public release of new chemical entity for pharmaceutical or agricultural purposes.

While these are distinct categories, there is considerable scope for moving between the categories. For instance, a licence might be exclusive for only a certain period, after which it becomes non-exclusive. The licensee might only be interested in getting a head start on competitors, rather than reserving exclusive rights for a longer period. Or there may be a mechanism in the agreement allowing for an exclusive licence to become non-exclusive in certain circumstances – for example, if the licensee fails to meet a certain milestone or is not sufficiently active in developing and marketing the technology – this is often called a 'march-in' right. And again the licensor might retain the right to issue further licenses for non-commercial purposes, or licenses to government agencies.

Sub-licences

A 'sub-licence' is a further licence, when the licensee of the original licence itself grants a licence to a third party. The sub-licence may extend to some or all of the rights granted under the original licence. The original licence may need to make clear whether sub-licences can be granted, and if so, to who, and on what terms or conditions. There may be issues such as protecting the confidentiality of licensed material, liability for use of the technology, or the interests of the licensor in granting direct licenses to the same third parties.

A sub-licensing program may be of considerable benefit to the licensor, as it will increase the scope of use of the licensed technology, and may be an effective way of exporting the technology to new overseas markets. The original licensor might retain an entitlement to a share of any royalties or other payments paid by the sub-licensee. The original licensor might retain the right to investigate and approve the eligibility of a sub-licensee, especially if the sub-licensee has no direct relationship with the original licensee.

Diligence and milestones

The licensee may be relying on the license as the principal mechanism for recovering its investment in research and for deriving benefits from the patent or other IP. So it may be important to the licensor to ensure that the licensee does everything they can to develop and commercialise the licensed IP. If a licensee gains an exclusive licence, subject to a royalty payment on profits, and then decides to shelve the technology for several years because its immediate interests lie elsewhere, then the whole value of the IP is lost to the licensor. So licenses will frequently include obligations on the licensee to develop and apply the licensed technology diligently and to meet specific deadlines. Where possible, certain defined points or milestones should be identified – possibly based on the business plan originally proposed by the licensee. The license could require the licensee to bring the product to the market as soon as practicable, and to continue to make the

product available to the public on reasonable terms. These obligations may also be built into sublicenses granted under the licence.

Payments and pricing:

A licence will normally involve a valuable 'consideration' – something of value which is given in exchange for the right to use this technology. It need not be financial consideration – it could be a right in exchange to use another technology (a 'cross-licence'), or valuable access to other facilities or resources.

There are many potential models for payment. It is always difficult to establish a value for intellectual property, even more so if it relates to unproven technology that will require a licensee to take a considerable commercial risk. The options boil down to lump sum payments, and royalties based on the extent of use of the technology. It is not unusual to see a mixture of both. For instance, there can be an initial lump-sum payment payable as soon as the licence is signed. Lump-sum payments can also be required after other specific events, such the grant of a patent covered by the licence, or on a regular basis, such as annual licence maintenance fees. Requiring lump-sum payments provides an incentive to work the licensed technology that may not be present if the license only provided for royalties. Yet royalties ensure that the licensor derives benefits from the scale of commercial success of the technology they have created. Royalties may be set as a certain percentage of gross sales of products using the technology or a percentage of profits, or may be linked to other signs of turnover, such as the number of units produced using the technology or the number of units sold.

If you are licensing out, especially to one licensee only, and you are relying on that licensee to produce the returns that will pay for your research, then you may need to structure the license to ensure they have an incentive actively to use the technology – if they are simply committed to paying a royalty if and when they choose to use your technology, they might not have an incentive to invest immediately in producing your technology, and they could leave it in the bottom drawer while they exploit other opportunities. As a stimulus to diligence, the licensee may have to pay a certain minimum royalty payment whether or not actual sales or use reaches that level.

Initial payments can also be credited against future royalties – in effect, an upfront payment can become an advance payment of minimum royalties. Or they can be separate from royalty payments, so that they are in effect a separate licensing fee, which is not credited against future royalty payments. Royalties need not be fixed – they can be scaled so that they are relatively high if the product is only produced in low volumes, but so they decrease if the licensee produces high volumes of the product. It might also be necessary to clarify when royalties fall due – when the licensee issues an invoice for the product, or when the licensee is actually paid by the purchaser of the product. There may also be provisions to allow for the royalty structure or level to be reviewed in the light of changing market conditions or other factors.

The need to monitoring the use of the invention and to ensure that royalties are paid, as well as checking on milestones and diligence obligations, can lead to requirements for record-keeping, access to accounts and records, and independent auditing of accounts concerning the payment of royalties and related data.

The approach taken should be realistic, especially in licensing biotechnology which can be subject to long regulatory delays and on which returns to the licensee can take a long time to realize. In licensing the Cohen-Boyer patent (discussed below and in *Module Two*), Stanford University issued broad, non-exclusive licenses – reportedly over 400 licenses altogether. It specified low initial fees and annual maintenance fees, and very low royalty rates (one half of one percent) to licensees who were early in signing up for licenses, to encourage early use of the technology. Later licensees could face higher royalties. Early licensees were also given credits for upfront payments, to be credited against future royalties.

This kind of licensing scheme lowers the incentive of infringers to go to court – as it will almost certainly be cheaper to take out a licence under a patent than face infringement proceedings. Earnings on this patent were very high, reportedly over $200 million altogether, and the technology was very widely used. While this may be a patent of exceptionally broad application and use, this illustrates how the approach taken to royalty and other payments, and an open licensing regime, can serve the dual objectives of making a new technology available to the public and to probably much higher than if even a very attractive exclusive licence were struck, because of the exceptionally broad applications of the patented technology.

Confidentiality:

There may be a requirement under the licence to keep certain know-how protected, and this may translate into specific obligations on the part of the licensee to provide protection and to restrict access to confidential information, in the same manner as a distinct non-disclosure agreement.

Copyright:

Apart from copyright protecting the licensed subject-matter (for example, if it includes computer software), the licence may clarify the copyright provisions covering manuals, data sheets or other documentation that are received and used as part of a licensed technology package.

Term

The license should specify how long the licensed right runs for. It could include an initial term, with option for renewal, subject to negotiations certain terms (such as royalty payments, or exclusivity) or demonstration of diligence. Alternatively, the license could be set to run for the life of the patent (potentially including any extension of the patent term).

Termination

The license may provide for termination before its expiry. This may arise in the event of breach of a license provision, or the bankruptcy, dissolution or insolvency of the licensee. The license could provide for termination in the event of the lapse or invalidation of the licensed patent right. There may be provision for termination by the licensee with due notice to the licensor, potentially subject to a termination fee.

Assignment

The license may need to set out on what terms the licensor or licensee can assign its rights and obligations under the license (for instance, clarifying what happens if a licensor sells its patent portfolio to a third party, and how the interests of an exclusive licensee can be preserved). It may provide for the licensee to give prior written consent before the licensor's rights can be assigned or transferred to a third party. It may also clarify whether, and under what conditions, the licensee can assign the licensed rights to a third party.

Improvements and grant-back rights

The licence may specify who will own IP rights relating to improvements and adaptations to the licensed technology arising from the licensed use of the technology. Equally, the licence may cover improvements made by the licensor to the original technology – the licensee may be entitled to access to any improvements (possibly subject to conditions, such as additional royalties or licence fees). There may be an agreement to cross-license improvements to one another, on a royalty-free basis. Unless the licensor is not interested in continued research in the field, the licensor would normally try to secure non-exclusive 'grant-back' rights, giving them access to any improvements made by the licensee – otherwise, the licensee might be able to get patent protection on these improvements and deny the licensor access to the best way of exercising their own invention. However, imposing licensing requirements for exclusive grant-back rights – i.e. unduly limiting the licensee's own capacity to exploit their inventions –is often cited in national law as illegal anti-competitive commercial behaviour (see below on 'abusive licensing practices').

Cross-licence

This kind of agreement involves an exchange of different entitlements – in a sense, each party is both licensor and licensee. So A grants B a licence to use A's intellectual property, and B grants A a licence to use B's intellectual property. This is one way of resolving complex patent litigation or competing claims to ownership of overlapping intellectual property rights.

Indemnification and warranties

These provisions cover such issues as who would defend (and pay for) any legal action against the licensee, in the event that the licensed use is claimed to infringe a third party's patent or other IP right. The licence might try to give the licensor an indemnity or safeguard against any claim of damages caused by legal action taken against the licensee regarding their use of the licensed technology. On the other hand, the licensor might be asked to give a warranty that they have the right to grant the licence, that intellectual property rights are valid, and that they are actually owned by the licensor without any conflicting claim. The licensor may need to warrant that they are unaware that the use of the licensed technology would infringe the IP rights of a third party - this might include an undertaking actively to investigate this possibility (such as through searches of patent documents). The licensee might be asked to give warranties that they will ensure they will continue to have the necessary expertise and resources to exploit the licensed technology effectively.

Required performance

If you are licensing out your IP-protected technology, you need to consider what level of performance you are expecting from the licensee, and what kind of guaranteed performance you would like to build into the licence agreement. To some extent, this is covered by the structure you choose for licence fees and royalties (discussed above), but there may be additional performance targets that can be set – for instance, minimum sales levels (potentially compared to previous years' levels), or relative to other markets or to competitors, such as a particular market share. This is especially relevant if you are contemplating granting an exclusive licence. You need to be clear whether the licence is really just an agreement to pay you a royalty when and if your technology is used, without any real obligation to exploit the technology; or whether the licence is meant to create positive obligations on the licensee to take active steps – or even their 'best endeavours' – to make sure the technology is fully exploited for your benefit and for the public benefit, and even to ensure that the technology is improved and refined as it is exploited.

The licensor may also have obligations to perform. The licensee may be expecting more than just a legal right to use the technology, and may be looking for more substantial assistance to exploit the technology effectively. So the license might involve obligations on the licensor to provide a certain level of training and technical support and advice, and to assist in the process of gaining regulatory approval to use the technology (for instance, assisting in providing the data necessary for the approval of a new pharmaceutical formulation). The licensor might also be required to advise the licensee of any research developments or improvements, or any new research outcomes that could adversely affect the viability of the licensed technology.

Publication of research

Licenses may contain conditions on the publication of research relating to the licensed technology, both to monitor developments in the technology and the licensed activities, and to ensure that prior publication does not destroy any future patent rights.

Maintaining IPRs

Licenses may cover obligations on maintaining a patent, especially in ensuring that an application is prosecuted to grant, and then ensuring that renewal fees are paid to keep the patent in force. Typically, an annual fee or some form of regular payment must be paid to the patent office to keep the patent in force – if it is not paid, then the patent lapses. These fees often increase during the life of a patent, and if a patent is held in different countries, the payments can become very considerable.

Because the licensee is gaining benefits from the patent – especially under an exclusive licence – they may be asked to contribute to, or to be totally responsible for, keeping the patent in force by paying these fees. In theory, a licence could provide that either party is responsible for paying renewal fees, although the licensor (and patent holder) may feel more comfortable ensuring payment, as it can be difficult (or after a certain time impossible) to reinstate a patent that has lapsed due to failure to pay renewal fees. The license can stipulate that the licensee pay a proportion of the IPR maintenance costs.

Especially if it involves a composite technology package – for example, combining patented technology with unregistered trade secrets or know how (confidential information) – then the license will need to be very clear about what happens when one of the components of the package changes status – say if a patent expired or was invalidated, while the related knowhow remained protected. This could involve a significant cut in the level of royalty payments, for instance, reflecting the decreased overall value of the licence.

Enforcing IPRs

The licensee of IP rights is often in a better position to monitor what its competitors are doing, and might be the first to find out about other parties infringing the patent or other IP right. Any licensee will be interested in preventing this activity, because it represents a competitor gaining an advantage over them, because they are avoiding licensing costs and other conditions on use of the licensed technology. Yet the licensor, as the owner of the IP, also has a fundamental interest in avoiding damage to the value of their IP caused by the infringing activities. IP litigation is expensive and time-consuming. Licenses can therefore clarify the respective roles and responsibilities of the licensor and licensee in enforcing the licensed IP rights.

Enforcing the licence and choice of law:

If either party fails to live up to the licence, there needs to be a way of enforcing the obligations undertaken by the licensor and licensee, and for compensating the other party for damage caused. Serious breaches of licences are not common, particularly if licences are well drafted and properly represent the shared interests and agreed working relationship of the two parties. Yet major licence disputes can be as complex and difficult as patent litigation. In addition, the licensor and licensee may be based in different countries, raising questions about what national law applies to the licence.

Licences therefore often contain provisions specifying what action should be taken in the event of a dispute between the licensor and licensee. It may provide for arbitration or mediation through a specified service as an alternative to litigation. And it will normally specify which law applies to the contract – such as the law of Indonesia or the law of Singapore, or in the case of a federal system such as the United States or Canada, it may be a state law, such as the law of the Province of Ontario.

Other licence terms

The licence can be more than just an agreement to permit the usage of the licensed technology in exchange for a payment. For instance, it might involve providing technical assistance, training and continuing transfer of technology that will be of assistance in exploiting the licensed technology. The license may cover such issues as marketing products produced by the licensed technology and requirements for the licensor's trade mark or certification mark to be applied. The license may also include undertakings as to compliance with ethical standards, environmental protection measures, and government regulations.

In addition, broader technology management issues may be addressed, so that the licensee does not impair the viability of the technology. In the example of Bt cotton in *Module Ten*, the technology license requires the user of the technology (the licensee) to undertake certain resistance management measures as part of an overall program to ensure that the insect pests do not build up resistance to the insecticidal properties of the licensed technology. If the licence covers biological material, it could contain provisions concerning the handling and use of the biological material, including obligations or restrictions concerning its export.

Preliminary documents: heads of agreement or letter of intent

A potential licensee may be unwilling to make firm and detailed commitments, for instance to pay a certain level of royalties or to cross-licence its own proven technologies, before an opportunity to evaluate the technology that is to be licensed. But they may be unwilling to invest in the evaluation process unless they have some confidence they will get exclusive rights to exploit the licensed technology. A confidentiality agreement or materials transfer agreement (see *Module Eight*) can be used to cover the initial disclosure for evaluation, so the future licensee can check the technology without damaging the interests of the party providing the technology or biological materials. But it might also be necessary to reach preliminary agreement on the commercial arrangements that will apply and to ensure that the future negotiations on the details of a licence have a solid basis of understanding. Even the commitment of resources to engage in negotiations on a licence requires some level of confidence that it is a worthwhile investment.

This leads to the commercial practice of agreeing on the general basis or overall framework of a future agreement, by means of documents variously called 'heads of agreement,' 'letter of intent,' 'memorandum of understanding' or 'agreement in principle.' You should be cautious when dealing with these documents. It may be unclear whether you are entering into a firm legal obligation – a binding legal contract – or just signalling your general willingness to do business and helping to shape and focus the detailed negotiations. If the negotiations fail, the other party might seek to enforce rights under an informal 'letter of intent' or 'agreement in principle' even if you thought it was not a strict legal obligation but just a general framework for discussions.

Abusive licensing practices

An IP holder is often not entitled to use the power of their IP rights to impose unfair terms on licensees who are interested in using the technology – national IP law or competition law often intervenes to make unfair, coercive or abusive licences illegal. The TRIPS Agreement acknowledges that 'some licensing practices or conditions pertaining to intellectual property rights which restrain competition may have adverse effects on trade and may impede the transfer and dissemination of technology.' Examples of these restrictions are exclusive grantback conditions (e.g. requiring a licensee only to grant licenses over any improvements to the licensor and no-one else), conditions preventing challenges to validity (e.g. requiring the licensee to avoid taking legal

action against a patent on the basis that it is not novel or is obvious), and coercive package licensing (e.g. requiring the licensee to use only the licensor's products in other areas as a condition of the license – stating, for instance, that a technology can only be licensed on the condition that the licensee purchases raw materials from the licensor).

Compulsory licences

A compulsory licence comes about when the holder of a patent is unwilling to license the technology or is otherwise viewed as failing to 'work' or exploit the patent for the benefit of the community. Under the patent law of many countries, there is provision for a court or similar legal authority to step in and issue a licence to permit a third party to make use of the patented invention. Because the licence is issued without the authorization of the patent holder it is known as a 'compulsory' licence. A compulsory licence may be required to deal with anti-competitive behaviour regarding patented technologies, to enable a patent holder of a dependent patent (a patent for a subsequent invention falling within the scope of an earlier patent) to exploit the invention, and for other general public policy reasons. Typically, compulsory licences are granted for limited purposes, are essentially restricted to the domestic (non-export) market, are non-exclusive, and are subject to payment of compensation to the patent holder.

Often included under the category of compulsory licences is non-commercial government use. The patent law of many countries provides for government agencies to make use of patented technology for non-commercial purposes, without prior authorization of the patent holder, again subject to payment of adequate compensation.

LICENSING, ENABLING TECHNOLOGIES AND THE PUBLIC INTEREST

The Cohen-Boyer patent on gene-splicing, discussed in *Module Two*, apart from representing a major technological advance, also raised important issues on appropriate licensing practices, given that this technology was fundamental to the development of the biotechnology industry and to the growth of research in this area. The following article, from the Internet magazine on biotechnology industry issues, *Signals* (www.signalsmag.com), discusses the licensing issues behind the patent. Another article from the magazine, *Stanford's DNA patent 'enforcer' Grolle closes the $200M book on Cohen-Boyer*, quotes the licensing officer as saying that "The philosophy of Stanford was that we wanted to make it available to mankind, and we felt it would never be exploited properly with an exclusive license," and comments that 'the university also sought to keep the buy-in modest so many companies were able to pick up the license.' At the same time, the patent was able to generate a very considerable amount of income to support further research.

Signals, 6/12/1998: The legacy of Cohen-Boyer

In the ongoing debate over how companies and universities should best profit from research tools, it's understandable that licensors would review how past research tools have been treated. Probably the most famous case of all is the Cohen-Boyer gene-splicing patent shared by Stanford University and the University of California system, which describes the fundamental technique for using restriction enzymes and plasmids to snip a gene from one organism's cells and insert it in a bacterium in order to produce a protein

What gets a bit muddled from time to time, though, are a few of the key details about just how the universities profited, and what their intent was. One often-heard inaccuracy, for example, is that Cohen-Boyer was offered royalty-free to all comers, in exchange for a nominal up-front fee.

There's no question the universities wanted to encourage the technique's broad use. "We wanted to spread it around for the whole world," says Floyd Grolle, the Cohen-Boyer patent "enforcer" for Stanford's Office of Technology Licensing since 1982. According to Grolle, the terms were quite clear-cut. There was an initial licensing fee of $10,000 and, after that, a minimum annual fee of $10,000. In addition, there was a royalty agreement, from which the minimum annual fee could be discounted. In other words, each licensee paid Stanford at least $10,000 up front and another $10,000 annually for the use of the Cohen-Boyer patent and more when the royalties from a successful product rolled in.

Part of the confusion is that unlike some of the research tools today which are a true intermediary step in the process, Cohen-Boyer is technically infringed whenever someone makes a recombinant protein using gene-splicing. Thus, the basis for the royalties is not "reach-through," but rather a technical infringement in the actual manufacture of a recombinant protein.

The other interesting question that arises over Cohen-Boyer is how different the development of the biotech industry might have been if Stanford and UC had licensed it exclusively. One version of the story says that Stanford University, which owned the patent with UC, offered it on an exclusive basis to Genentech, Inc. of South San Francisco and decided to go the non-exclusive route only when Genentech didn't offer enough money. The other version of the story is that Genentech wanted exclusive rights, but Stanford, which was handling the negotiations of the two schools, never offered them.

According to former Genentech counsel, Thomas D. Kiley, he and Genentech CEO Robert Swanson met with a Stanford official in an effort to procure exclusive rights to all mammalian polypeptide applications of the Cohen-Boyer patent. Genentech presumably had the inside track, since Genentech co-founder Herbert Boyer of UC was half the team that invented Cohen-Boyer. Indeed, the meeting went very well and as far as Kiley was concerned, "We thought we had them."

But no such luck. Neils Reimer, head of Stanford University's licensing group, quashed the notion and the fate of biotech took a definitive turn and Cohen-Boyer patent was made available to whomever wanted it.

The upshot was that the relatively low fees meant that almost anyone could acquire rights to the basic biotech patent, making possible, in part, the myriad of biotech start-ups that began in the early '80s and continues to this day. At the time of its expiration on Dec. 12, 1997, the Cohen-Boyer patent had 380 licensees, according to Grolle. During its 15-year lifetime, the total number of licensees was 480. Which was precisely what the universities wanted, says David Aston, associate director of the Office of Technology Transfer at UC Berkeley and keeper of the Cohen-Boyer files. A great deal of thought and discussion took place regarding the licensing of the Cohen-Boyer patent, Aston says. "This is a strategy that evolved over a couple of years," he says. "It's consistent with the university view of technology use -- an archetype for university models," Aston says.

9.5 Enforcement of Intellectual Property Rights

Intellectual property rights can be very valuable commercial rights for inventors, creators and researchers. Intellectual property rights are legal rights to do certain things in relation to an invention or creation. In general terms, intellectual property rights are infringed if someone exercises an intellectual property right without the permission of the owner of the right. In order to protect the value of intellectual property rights effective legal remedies must be available if intellectual property rights are infringed.

Intellectual property rights are of limited value unless they are effectively enforced. Without enforcement, there are no real deterrents for infringers or remedies for those whose rights are infringed. The legal authorities do have some role in enforcing intellectual property rights, but this is often limited, and for infringement of rights such as patents, plant breeders rights and trade secrets, you would normally have to take action yourself to take the infringing party to court. The same practical commercial considerations that apply to obtaining and managing IP rights also apply to enforcement – in some cases, the possibility of taking court action could act to encourage the infringing party to take out a licence to use your technology. This would save you the expense and the uncertainty of a protracted court case, and could provide you with a good financial return.

The procedures for enforcement of IP rights differ widely between countries, because they have much more to do with the general legal system than other aspects of IP rights, such as examination and grant of rights by a patent office. The TRIPS Agreement (see *Module One; Introduction to Intellectual Property* and *Annex One*) has established some general principles for IP enforcement which are reflected in the laws of many countries, so this discussion will focus on the TRIPS provisions to give an overall picture of how enforcement operates.

One basic distinction in enforcement lies between more those IP infringements which tend to be infringed widely, potentially by many different people and on a large commercial scale, and general IP rights. In the first category are pirated copyright works and counterfeit trade mark goods. TRIPS, for instance, specifies that the government or legal authorities need to have a more active role in dealing with these infringements than, say, for patents and plant breeders' rights. So the state often has an active role in tracking down and prosecuting those who infringe copyright and trademark rights on a commercial scale, whereas for patents it is normally up to the patent holder or licensee to take an infringer to court.

Enforcement measures required by TRIPS

As discussed in *Module One: Introduction to Intellectual Property*, the TRIPS Agreement differs from earlier international intellectual property treaties in several ways; this includes having specific provisions for effective enforcement of IP rights in national laws. The main enforcement provisions in TRIPS include:

- the general obligations under the TRIPS Agreement, which relate to the provision of fair enforcement procedures
- civil remedies, including injunctions, damages and provisional measures
- criminal procedures, which are compulsory for intentional trade mark and copyright piracy on a commercial scale and optional for other kinds of intellectual property, such as patents

- special border enforcement measures to stop counterfeit trade mark and pirated copyright material coming into a country, border enforcement measures are optional for other kinds of intellectual property, such as patents

General enforcement obligations under TRIPS

The TRIPS Agreement provides for a range of general obligations in relation to the enforcement of intellectual property rights. The purpose of these obligations is to ensure that the enforcement measures are effective, and that certain basic principles of due process are met, so that enforcement is fair and balanced, and does not impede legitimate trade.

Remedies must be timely and deter further infringements

TRIPS requires that enforcement procedures permit effective action against any infringement of intellectual property rights, and that the remedies available are expeditious in order to prevent infringements. A legal system that enables timely initiation and execution of legal processes is particularly important for effective enforcement of intellectual property rights because the information that intellectual property protects is often easy to copy and spread quickly.

The remedies available must also be severe enough to deter further infringements. These procedures must be applied in a way that avoids the creation of barriers to legitimate trade and to provide for safeguards against their abuse.

Enforcement procedures must be fair

TRIPS provides that enforcement procedures must be fair and equitable, and may not be unnecessarily complicated or costly, or entail unreasonable time-limits or delays. Decisions in enforcement cases must be based on the merits of a case. Decisions should preferably be in writing and reasoned, and be made available to the parties without undue delay. Decisions on the merits of a case must be based only on evidence in respect of which the parties were offered the opportunity to be heard.

Parties to a proceeding must have an avenue of appeal, unless the case was criminal in nature and the accused was acquitted. TRIPS does not require a special judicial system for the enforcement of intellectual property rights distinct from the normal court system. Finally, TRIPS creates no obligations with respect to the distribution of resources as between enforcement of intellectual property rights and the enforcement of law in general.

Example – enforcing a patented invention for making house paint

For example, imagine that you own a patent for house paint that dries very quickly. It took you 8 years to develop the process and cost you thousands of dollars to patent your invention in Australia, the US and Indonesia. Just as you started to distribute the paint yourself in Australia you found out that your paint is being sold cheaply to the painting trade in Sydney by a company trading as *Cheap Paints*. You also suspect that *Cheap Paints* are exporting tins of infringing paint overseas. Obviously you need to take legal action against *Cheap Paints* to enforce your rights, otherwise, there would be no market left for you to get any financial return on your invention. The kinds of remedies you could take against Cheap Paints are set out in this Module.

CIVIL REMEDIES

Fair and equitable procedures

Defendants in civil matters must be notified in writing that they are being sued, informed of the claims made against them in sufficient detail and have the right to be represented by independent legal counsel. The parties are entitled to present all relevant evidence, while confidential information must be identified and protected.

Injunctions

TRIPS requires that courts be capable of ordering injunctions. An injunction is a court order compelling a party to stop infringements, or prevents it from infringing in the first place. Injunctions can also be ordered to prevent imported infringing goods from entering into domestic distribution channels.

Example - use of an injunction against infringing sale of patented house paint

Remember in the above example that *Cheap Paints* were selling cheap tins of your patented house paint in markets in Sydney. This was a major problem for you because the price of your paint was higher than the pirated paint and *Cheap Paints* were destroying your market. Unlike you, *Cheap Paints* did not have to recoup all the costs you incurred in developing and patenting the new paint so they could afford to under-cut your price.

In this case, an effective remedy for you to use against *Cheap Paints* is an injunction - a definitive order issued by the court, which the infringer is bound to follow. An injunction could order *Cheap Paints* to stop selling the infringing paint and give you back the market for selling your patented paint.

Damages

TRIPS requires that courts must be able to order an infringer, at least if he or she acted in bad faith, to pay adequate damages to the intellectual property right owner (TRIPS Article 45(1)). Damages compensate the intellectual property owner for the damage caused by an infringement. Courts must also be authorised to order the infringer to pay the right owner's court costs, including lawyers' fees (TRIPS Article 45(2)). In appropriate cases, the courts may allow the plaintiff to recover profits made by the defendant through the unauthorised use of the plaintiff's intellectual property (an 'account of profits') and/or pre-established damages even where the infringer acted in good faith (TRIPS Article 45(2)).

Example - damages for infringing sale of patented house paint

Another remedy for you to use against *Cheap Paints* is the remedy of damages. Damages can be used in addition to an injunction. In the previous example it was important for you to get an injunction against *Cheap Paints* to stop them from selling infringing versions of your house paint. This enabled you to sell your patented paint yourself and get the financial benefits from sales of your patented invention. However, you could also take an action against *Cheap Paints* for damages to compensate you for the loss that you suffered because of their infringing sales of your patented paint. For example, you could get damages to compensate you for lost profits during the time that the infringing paint was sold. You may also be able to obtain compensation for any loss of reputation that *Cheap Paints* may have caused you if, for example, its paints were of an inferior quality and consumers believed that you produced it. *Cheap Paints* may cause you serious financial damage if consumers have stopped buying your products.

Other remedies

TRIPS provides for other remedies in addition to injunctions and damages. In order to create an effective deterrent to infringement, TRIPS requires judicial authorities to have the authority to order infringing goods to be disposed of outside the channels of commerce, or, where possible under domestic law, destroyed. Similarly, it must be possible to dispose of materials and instruments predominantly used in the production of the infringing goods.

Provisional measures

As noted above, TRIPS requires that enforcement procedures must permit effective action against infringements and include timely remedies. However, as complete judicial procedures can take a quite a long time, TRIPS requires that judicial authorities be able to provide provisional relief for intellectual property owners in order to stop an alleged infringement immediately while the case is fully considered. This may mean that a judge can grant an injunction almost straight away, which may prevent the defendant trading in the allegedly infringing goods until the final trial decision is handed down. It is imperative that swift (and in some cases pre-emptive) action can be taken to prevent infringements or stop them quickly.

Provisional measures must be available in two situations. First, it must be possible to prevent an infringement from occurring, and to prevent infringing goods from entering the channels of commerce. This includes preventing imported infringing goods from being dispersed into domestic distribution channels immediately after customs clearance. Second, provisional measures must be available to preserve relevant evidence relating to the alleged infringement. This, for example, may be in the form of an order compelling the defendant to allow the plaintiff and his lawyers to enter his or her business premises to secure evidence. In many common law countries, this is called an *Anton Piller* order. This remedy is important in intellectual property cases because it is often easy for the defendant to dispose of evidence on short notice (sometimes it might be as easy as deleting files on a computer).

In order to be effective, provisional measures may require that action be taken without giving prior notice to the other side. Accordingly, the judicial authorities must be able to order provisional measures (such as injunctions) in the absence of the defendant where appropriate, particularly where any delay is likely to cause irreparable harm to the intellectual property owner, or where there is a risk of evidence being destroyed.

You may think that these procedures are unfair on the defendant and that the presumption of innocence is discarded because he or she is punished before the trial has taken place. This has been a concern in national legal systems, and TRIPS requires that provisional measures must contain safeguards against abuse of such measures. For example, the judicial authority may require the applicant to provide a security or equivalent assurance sufficient to protect the defendant and to prevent abuse. This may be payable to the defendant if the plaintiff loses the case. Some countries have made injunctions more difficult to obtain by, for example, requiring that the plaintiff prove that the defendant has a serious case to answer and to establish that damages will be an inadequate remedy if the injunction is not granted.

There are other provisional measures which TRIPS does not mention, but which are provided for under the laws of many countries. For example, if a plaintiff is afraid that defendant will move its assets out of the jurisdiction to avoid paying compensation, he or she may be able to convince the court to freeze the assets of the defendant for the duration of the trial. This is called a *Mareva Injunction* in some countries.

CRIMINAL PROCEDURES

Civil proceedings, initiated by the right holder, are often considered the more appropriate approach for dealing with infringement of IP rights. They give the right-holder the opportunity to obtain damages to compensate his or her losses, lost profits and legal costs if the case is successful. However, criminal proceedings apply to infringement of some IP rights. In this case, the state's legal authorities are responsible for taking the infringer to court, and the court imposes a penalty such as a fine or, in extreme cases, imprisonment.

TRIPS only requires that criminal procedures need be provided for intentional trademark counterfeiting or copyright piracy on a commercial scale. The remedies available for such crimes must include imprisonment and/or monetary fines. The monetary fines must be enough to deter future counterfeiting.

TRIPS allows Members to provide criminal procedures and penalties in other cases of infringement of intellectual property rights, in particular where they are committed intentionally and on a commercial scale. That is, it is not mandatory for countries to provide criminal procedures for intentional infringements of patents and plant breeders' rights, although some countries may choose to (in practice, this is unusual).

There are advantages and disadvantages to using criminal procedures. On the one hand, the government will probably run the trial, and so the costs to the inventor of bringing the action are minimal. But on the other hand, the penalty obtained from a conviction will usually go to the state. This means that, if the right-holder has suffered substantial losses, criminal proceedings do usually not directly enable them to recoup their losses.

Special Border Enforcement Measures - Customs

In relation to trade marks and copyright, TRIPS also provides for special border enforcement measures. The purpose of the border enforcement measures is for intellectual property owners to be able to get assistance from customs authorities to prevent the importation of counterfeit trade marks and copyright goods (TRIPS Articles 51-60). These provisions also include safeguards to prevent the abuse of the border enforcement provisions by trade mark and copyright owners.

Different roles in IP enforcement

Effective enforcement is vital if the IP system is to function properly. If there is no real risk of legal sanctions in the event of infringement, the IP right loses its value. Enforcement is not the role of any one body. It is a cooperative task potentially involving enforcement agencies, including the courts, police and customs. National intellectual property offices do not usually have a direct role in enforcing intellectual property rights, although in some countries they do have a role, either in providing expert advice or in coordinating investigation and prosecution of infringements.

Ultimately, it is the responsibility of the right holder to enforce their own rights. In many cases, this is the only option. Even if there is the possibility of criminal proceedings or border control measures, the right holder may need to initiate the complaint and assist with the provision of evidence and testimony. For IP rights most associated with biotechnology, such as patents, plant breeders' rights and confidential information (trade secrets), civil actions initiated by the right holder are often the only option. The potential cost and risks associated with IP enforcement should be built in to your strategic planning. Infringement insurance is a possibility, and may need to be investigated. But you should also try to involve others with an interest in the IP rights – for instance, an exclusive licensee, who might have even more interest in seeing the licensed IP right effectively enforced than you do. Provisions on who is responsible for enforcement are therefore often included in license agreements and joint venture agreements.

9.6 Summary of Module Nine

What is the best way to exploit your IP rights?

You need to make good commercial decisions to benefit from your intellectual property rights. Intellectual property rights do not guarantee you a financial return on your invention, but they can assist. Which commercial model you choose to exploit your rights will depend on the value of your invention and how much money and time you have to exploit your rights. Options are:

licensing your intellectual property rights: a licence is a grant of permission to exercise any rights of the patent owner, licences can be exclusive or non-exclusive

selling (or assigning) your intellectual property rights: in contrast to a licence, an assignment of intellectual property rights is the sale of those rights

joint venture with commercial partners to manufacture and market your invention, and

set up your own company to manufacture and market your invention.

Key clauses in a licensing agreement

A licensing agreement is a common way to exploit intellectual property rights. Key clauses in them relate to: the name of the intellectual property rights licensed, ownership of the intellectual property rights, royalty rates, which territory the licence applies to, whether the licence is exclusive or non-exclusive, who will pay the costs of maintaining the patent rights, confidentiality and publication issues, insurance, release and indemnity and dispute resolution and termination.

Enforcement of intellectual property rights

It is important to enforce your intellectual property rights to protect the value of your intellectual property rights. National legal authorities do have a role in enforcement of IP rights, but as a rule it is up to the owner of IP rights to initiate action against infringers. Licensees may also have a role in enforcement. Effective legal remedies must be available to deter and punish infringements of intellectual property rights. The options for enforcing your intellectual property rights include:

civil remedies including **injunctions**, which are court orders to stop infringements, and **damages**, which compensate the intellectual property owner for damages caused by the infringements

criminal procedures, which are compulsory for intentional trade mark and copyright piracy on a commercial scale and optional for other kinds of intellectual property, such as patents, and

special border enforcement measures to stop counterfeit trade mark and pirated copyright material coming into a country, border enforcement measures are optional for other kinds of intellectual property, such as patents.

Typically for biotechnology IP, such as patents, plant breeders' rights and trade secrets, the only option for enforcement will be for the right holder to take legal action in the form of a civil procedure. This can be very expensive, and should be factored in to the strategic management of IP rights, and is often addressed in licenses or agreements concerning IP rights.

9.7 Group Exercises - Module Nine

Module Nine provides information about licensing and enforcing intellectual property rights. Please discuss Module Nine with your fellow participants and prepare answers to the following questions.

Exercise 9.1 Discussion of commercialising research IP

This module includes a description of the licensing strategy employed for the Cohen-Boyer patent, and an interview with François Bourgeois covering some of the issues involved in public sector use of the IP system. Discuss the various approaches covered in these materials within your group and prepare a brief report on its relevance to your own research work or policy interests.

Exercise 9.2 - licence agreements

Rana is a researcher who works for the Indian Institute for Biotechnology. He recently invented a new headache tablet which was given the trade name *Credence*. The Institute applied for and got a patent for Rana's invention in India, Malaysia and Indonesia.

After the patent was granted the Institute checked out commercial interest in the *Credence* headache tablet. Initially the Institute wanted to sell the product as it wanted a large upfront payment for the patent rights. However, it decided that it would be better to licence use of *Credence* on a trial period instead. The pharmaceutical company called "Indian Medicine Ltd" wants a licence to manufacture and sell *Credence*. Sonika is a lawyer who works for the Indian Institute for Biotechnology. She has been asked to prepare a licence between the Institute and Indian Medicine Ltd.

What issues should the licence should cover?

Exercise 9.3 – comparing exclusive licences, non-exclusive licences and assignments

With Sonika's help, the Indian Institute for Biotechnology gave Indian Medicine Ltd an exclusive licence to manufacture and market *Credence* in India for 5 years from 2000-2004.

(i) Can the Indian Institute for Biotechnology give the pharmaceutical company called "Better Medicines" an exclusive licence to manufacture and market *Credence* in Indonesia for 5 years from 2000-2004? Why?

(ii) The Indian Institute for Biotechnology also gave Malaysian Medicine Ltd a non-exclusive licence to manufacture and market *Credence* in Malaysia for 5 years from 2000-2004. Is it possible for the Institute to grant a separate non-exclusive licence to a different company called "KL Pharmacy Products" to manufacture and market *Credence* in Malaysia for 5 years from 2000-2004? Why?

(iii) Instead of giving an exclusive licence, imagine that the Indian Institute for Biotechnology gave Indian Medicine Ltd an assignment of all their patent rights for *Credence* in India for the whole term of the patent rights.

Could the Indian Institute for Biotechnology then give an exclusive licence to the company called "Delhi Medicines Ltd" to manufacture and market *Credence* in India for 5 years from 2000-2004? Why?

After the assignment to Indian Medicine Ltd, could the Indian Institute for Biotechnology licence anyone to use *Credence* in India for the term of their patent rights? Why?

(iv) What is the difference between an assignment and a licence?

Exercise 9.4 - remedies for IP infringement

As noted above, the Indian Institute for Biotechnology has patented its new headache tablet called *Credence* in India, Malaysia and Indonesia. The Institute had entered into a joint venture with a major pharmaceutical company called "TechMED" to manufacture and sell Credence in parts of India and Indonesia.

When one of the employees of the Institute was on holidays in Uttar Pradesh in India he saw an advertisement in a local newspaper for a supermarket chain selling *Credence* for half the price that the Institute and TechMED were selling it for. He knew that this was an infringement of the Institute's rights. He notified the Institute.

What are the names and features of the enforcement actions the Institute could take against the supermarket chain? Which Articles in the TRIPS Agreement provides for these remedies?

Exercise 9.5 - border enforcement of intellectual property

One of the case studies in *Module Ten* deals with a hypothetical invention of "Eternal® papayas". This new variety of fruit was created using biotechnology techniques. The invention of the new papayas has been patented and the name "Eternal® papayas" has been registered as a trade mark.

Imagine that infringing case loads of the "Eternal® papayas" have been illegally imported into Australia. The case loads of fruit are infringing because they were made without the permission of the patent owner, are being imported without the permission of the patent owner, and the trade mark is also being used without permission.

Does TRIPS require any border enforcement remedy for the patent infringement? Does TRIPS require a border enforcement remedy for the trade mark infringement?

FOREIGN AFFAIRS AND TRADE

AUSTRALIA

AusAID the Australian Government's overseas aid program

Module Ten

Case Studies on Commercialising Research

Intellectual Property and Biotechnology

A Training Handbook

Contents: Module Ten

10.1 Objectives for Module Ten

By the end of this Module you should have an understanding of:

- Approaches to collective discussion of the trend towards commercialisation of research conducted by public institutions, including through conducting practical workshops
- Some issues that arise in taking a biotechnology invention to market, including practical experience from the hypothetical "Papayas" case study in:
  - identifying the relevant issues before commercialisation of an invention
  - analysing these issues, and
  - deciding whether to market an invention
- The steps taken to commercialise research in the Bt cotton case study including how Monsanto (the patent owner):
  - developed the Bt gene
  - collaborated with CSIRO to create new cotton varieties using the Bt gene
  - obtained the necessary regulatory approvals, and
  - licensed the use of the Bt technology through a technology users' agreement

10.2 Workshop on IP management for researchers

Training in IP management

The focus of this Module is on group training in the management of IP rights. It describes two case studies, one hypothetical (Eternal papayas) and one an actual product (Bt cotton). These are designed to be used to promote group discussion of the various approaches that can be taken in commercialising biotechnology research, and the sort of considerations that need to be taken into account. Before developing these specific case studies, this Module discusses another approach to training in the management of IP rights: holding a workshop or training seminar, using the comparative expertise and practical knowledge of a few researchers who have been involved in developing research outcomes for the public, either through the commercial market or by other means.

Making effective use of the IP system to support research involves a complex set of new skills and careful program management. Unlike the technical aspects of patent law, for example, this is an inherently practical matter that cannot be reduced to a well-defined set of principles. While there are general guidelines, how those guidelines are applied in such a way as to stimulate and support research is a more important issue.

There is no substitute for direct experience in the field, including through sharing experiences of successes and failures in bringing new biotechnology to the market place. A workshop or training seminar is one useful approach to developing the necessary awareness and skills, if a number of individuals are available with suitable backgrounds in research and commercial environments – ideally, there should be a mix of personnel, from public research institutes, private technology companies, universities, and technology brokers or venture capitalists.

To illustrate this approach, this part of Module Ten describes a recent APEC workshop which drew together researchers from several newly-commercialising research institutes and researchers and IP policy officials from a range of developing countries. These were public sector research institutes with a continuing public focus, and a research organisation that had recently become a public company.

Workshop objectives

The objectives of the workshop were:

- To consolidate the topics covered in technical training on IP law and practice;
- To highlight areas of practical concern for research and technology management; and
- To exchange and compare experiences in the use of the IP system by research institutes, with a view to developing practical guidelines involving representatives of research institutes.

The participants who led the discussion were asked to draw on their own experience in discussing these questions:

- What have been the strategic IP considerations in your research and development programs?
- What were your IP success stories – what were the elements of success?
- What have been the failures – inventions that were not effectively protected by IP and were taken up successfully by others, or inventions that weren't put onto the market because of IP management issues?
- Is it inevitable in a research program to have a mix of IP successes and failures?
- Has lack of awareness or limited IP-related skills led to lost opportunities?

- What are the knowledge gaps and training needs? Do researchers, research managers, technology managers and government officials concerned with technology issues need specialized IP training? What kind of training programs have been successful?
- Does the pressure to commercialise and to secure IPRs change research priorities and direction?
- How can a research institute balance its policy interest in producing beneficial new technologies with a patenting and licensing program? What strategies can be used to disseminate new technology to the public?
- What ethical and cultural issues have arisen in developing and commercialising biotechnology? How have these been addressed?
- How can managers promote an innovation culture, and balance scientists' interest in exchanging ideas and publishing their research, with a confidentiality regime to protect new IPR?
- Is there a danger of pursuing a patent as an end in itself, rather than as part of an overall research and commercialization strategy?
- Have IPRs been used effectively to secure funding and the enabling environment for further public-interest research?
- What models have been effective for partnerships between research and business interests in financing, planning and commercializing research in the biotechnology field? What do these models tells us about who should own individual IPRs, and how they should be licensed, financed and enforced?
- How have patent information resources relating to biotechnology been used:
  - in planning research and looking for new research opportunities?
  - to secure freedom to operate in research programs?
  - in identifying potential research and investment partners?
  - to gain access to new technologies, through licensing or cross-licensing?
  - to monitor technological developments?

Discussion of the issues

In one example, concerning the development of a vaccine, the market leaders including major pharmaceutical companies were concentrating on identifying genetic structure, while a much smaller company was able to patent important methods. This led to a valuable partnership and a joint program to develop a vaccine, with a substantial royalty stream going to the smaller company. The key message to researchers was that if you have a valuable piece of the big pharmaceutical companies' puzzle, and you have intellectual property rights over it, then you can be in a strong bargaining position.

A second example raised the question of researchers' independence. A small company in association with a university explored a link between a virus and a form of cancer. A relatively small research budget was greatly eclipsed by the resources of the major companies. Research into this link produced patent rights, which were successfully licensed to a major pharmaceutical company. The question was raised as to whether private companies had the luxury to engage in original research involving linkages that do not appear to have a direct commercial application. The pressure to justify research as commercially viable could limit research directions. The effect

of this was to introduce an additional step into research planning – originally, the question was whether the project was scientifically sound and technologically viable; now there was an additional consideration – could the project have IP potential and could it generate income. For scientists, this change of focus had significant ramifications.

- It could limit the scope of research.
- It was necessary to keep effective and accurate laboratory notebooks, which could be a difficult cultural change for researchers.
- It called for precise timeframes on the part of scientists who may not be effective at managing their time.
- It meant that scientists had to curb their impulse towards publishing and sharing information on research developments, and had to take a more cautious approach at least in the initial phases of research.

A third example concerned a not-for-profit research institute. This had only recently developed a focus on IP. This was because:

- changed economic conditions meant that funds available from private charitable trusts were reduced and no longer sufficient to support research; and
- clinical trials to prove the safety and efficacy of new treatments, and to achieve regulatory approval, were extremely expensive; it had proven impossible to obtain financial backing to bring a new product onto the market without IP protection.

This meant that it was actually not possible to make the benefits of health research available to the public without a commercial partner and a program of IP management. Some of the considerations that had to be taken into account when introducing an IP program were:

- Equally important as patenting were material transfer agreements, confidentiality agreements, research and collaborative agreements.
- Collaborating scientists had to be prepared to discuss financial arrangements early, to ensure that there is a clear understanding from the beginning.
- Patenting should be done as soon as possible – this also helps to meet the scientists' interest in publishing their work at an early stage; at the same time, the patenting program should take into account possible technological changes that might yield broader applications for the invention.
- Not all researchers needed to have detailed training on IP – overdoing it could be counterproductive – but all needed to have a general understanding of IP principles and processes.
- The commercial aspects shouldn't be overemphasized – it remained fundamentally important for the research program that scientists should be able to exchange ideas and have the freedom to maintain their creativity.
- To capture all IP generated by an institute, a system could be established to scan all abstracts before they are submitted to journals for publication; this could be linked to a patent committee which would make strategic decisions about patenting.

Overall, those managing research institute should consider how to improve the use of the patent system without preventing or deterring researchers from continuing basic research. To the contrary, effective use of the IP system can be used to sow the seeds for future research, and to help direct research towards successful outcomes, without needlessly repeating work done elsewhere.

Your workshop

You may wish to conduct similar workshops to facilitate training in this area. There is no one solution to the challenges of blending research with commercialisation, but a discussion of the practicalities of IPR management and the solutions applied by others may assist you and your colleagues to work out your own solutions. The following case studies are provided to assist such group discussions – for example, you could consider how your own institute, working within your own country's legal and commercial environment, would tackle these case studies, and use this as a springboard for general discussion about IPR management..

10.3 Group Exercise on Eternal â Papayas

This case study is about the hypothetical invention of transgenic Eternal® papayas within a fictional research institution. It will give you a chance to consider what practical steps you might need to take before commercialising an invention, focussing on how to get "freedom to operate" – in other words, to work out whether you can commercialise a new technology without running into problems with intellectual property rights that others might hold.

The Commercialisation Checklist for Eternal â Papayas

✓ **Develop a combined R&D and IP strategy**

The South East Asian Institute of Biotechnology requires all researchers to develop a combined research and development and intellectual property strategy, with a focus on working with local commercial partners to promote the availability of research outcomes for the benefit of local producers. Agus, a scientist with the Institute, prepared such a strategy before starting research in to papayas. The strategy aimed at getting useful IP rights and ensuring he could commercialise any invention if his research turned out to be successful.

The IP strategy involved aiming at a mix of patents and plant variety rights, and trade mark protection, and required research into different approaches to allowable subject matter for patents in different markets, particularly the differences on patenting plant inventions.

✓ **Do a patent survey**

With the assistance of professional patent searchers, Agus undertook extensive searches of patent databases to see what research had already been done that is relevant to his project, to work out what other researchers and institutions were doing work that might be useful for him, and to check for existing patent rights that could interfere with his proposed research techniques and the development of his research outcomes. This helped focus his research planning to ensure that he didn't repeat earlier research, he could approach potential research collaborators and commercial backers, and he knew in advance about potential problems with existing patent rights. He also surveyed relevant plant variety rights, because these might also be relevant to his work on papayas.

✓ **Create a new invention**

After many years of research Agus developed the Eternal® papaya which has an exceptionally long shelf-life, so that it can be enjoyed fresh after being stored and transported for long periods. This saves cost in freighting papayas to export markets.

✓ **Protect confidentiality until patents are applied for**

Part of Agus's R&D and IP strategy was to keep his invention in confidence until a patent application had been made. This helped the Institute get patent protection for Eternal® papayas

in Indonesia, Malaysia, Australia, Europe and the US. Agus's lab notebooks helped to prove he was the first to invent Eternal® papayas, in case it was necessary to defend patent rights in the US.

✓ **Keep track of costs**

Agus and the Institute kept a record of all the costs of developing Eternal® papayas, including the costs of getting advice from a patent attorney and commercial adviser. They knew that this would be useful in their dealings with their commercial partners and in ensuring the process would contribute to the future work of the Institute.

✓ **Do business research before commercialisation**

As the patent owner, the Institute developed a business strategy, which set out goals and included a budget. It researched demand for the invention and decided to market the invention in the countries in which Eternal® papayas is patented. It also hired a consultant to investigate the health and safety regulatory approvals would be needed before Eternal® papayas could be sold, and developed a plan for financing these approval procedures by involving a commercial partner.

✓ **Decide which model of commercialisation is best for you**

The Institute did not have the money or the business skills to market Eternal® papayas by itself. So, it licensed a company called "PT Biovarietas" to market the invention in return for royalties, which would be shared with Agus because he was the inventor.

✓ **Establish freedom to operate**

There is still one important consideration to take before Eternal® papayas can be fully developed and commercialised. The Institute needs to ensure that PT Biovarietas will have "freedom to operate". That is, it needs to check whether marketing the invention will infringe the rights of any other people (called "third parties"), and deal with the legal or technical implications of any third party rights. In the exercises below you will work out if there is freedom to operate to market Eternal® papayas.

The Steps to Ensure Freedom to Operate for Eternal â Papayas

This exercise focusses on assessing whether the Institute, and its commercial partner, PT Biovarietas, have freedom to operate in putting Eternal® papayas onto the market. More details about 'freedom to operate' are in *Module Eight: Researching and Intellectual Property*.

The technologies used in Eternal â papayas

- Agrobacterium-mediated transformation
- Binary Vector System to move constructs into plants
- Chimaeric gene constructs: trait / selection including:
  - CaMV 35S promoter
  - nos promoter region
  - ACC synthase coding region
  - nptII coding region
  - 3' ocs terminator region
  - 3' nos terminator region
- Down-regulation using co-suppression

The proposal for commercialisation of Eternal â papayas

The Institute knows that PT Biovarietas proposes that the transformation will be carried out locally in Indonesia. The plants also will be regenerated and grown locally. Some fruit will be consumed locally and the remainder will be exported.

As noted above, the target markets for Eternal® papayas include Malaysia, Singapore, Australia, Europe and the US. The Institute proposes that exports will start in 2007 to Malaysia, Singapore and Australia, then in 2009 to Japan, Europe and the US.

Exercise 10.3.1 - identify the technologies used in Eternal â papayas

The first step in working out whether the Institute has freedom to operate is to list all the technologies used in Eternal® papayas. What are all the technologies used in Eternal® papayas (see the list that is set out above)?

Exercise 10.3.2 - identify the relevant existing patents for Eternal â papayas

Secondly, the Institute needs to carry out patent searches to identify all the potentially relevant patent specifications for the Eternal® papayas technology. Potentially relevant patents are patents on any of the technologies used in Eternal® papayas. The Institute needs to get copies of the specifications and claims. For this exercise, the patents in potentially relevant technologies are summarised in Attachment 1 and the relevant claims are at Attachment 2.

Exercise 10.3.3 - interpret the scope of existing third party patents

The third step is to interpret the scope of the claims of the relevant existing patents and decide whether commercialising Eternal® papayas would infringe the rights of third parties. You need to work out whether the Institute needs a licence from anyone to commercialise Eternal® papayas. Remember to check the term of the grant of patent. The patent term might be finished or it might be nearly finished. You will need to look at the table at Attachment 1 to see the potentially relevant patent specifications filed. You will also need to analyse the claims in these patents that are at Attachment 2.

(i) Can Eternal® papayas be exported to Malaysia? Why? Are any third party licences needed? From whom?

(ii) Can Eternal® papayas be exported to Australia? Why? Are any third party licences needed? From whom?

(iii) Can Eternal® papayas be exported to the US? Why? Are any third party licences needed? From whom?

(iii) Can Eternal® papayas be exported to the EU? Why? Are any third party licences needed? From whom?

10.4 Case study: The commercialisation of Bt Cotton

Cotton containing the Bt gene – known as 'Bt cotton' - was among the first genetically modified crops in widespread commercial production. This case study sets out the approach taken by the multinational company Monsanto to commercialise Bt cotton in Australia, through various legal agreements with owners of other intellectual property rights. Bt cotton has been commercialised in Australia under the trade mark INGARD® and in many other countries under the trade mark BOLLGARD®.

Cotton production is one of Australia's biggest agricultural industries, contributing around $900 million a year in export income. INGARD cotton was the first genetically modified crop approved for commercial release in Australia. Monsanto, which held a patent on the Bt gene, developed a unique commercialisation strategy to get a viable financial return on its R&D expenditure in the seed market.

This case study considers:

- the nature of INGARD cotton;
- the kind of intellectual property protection applicable to Bt cotton;
- the health and safety regulatory issues faced by Monsanto in commercialising the Bt gene;
- the key players with whom Monsanto joined to commercialise the Bt gene in cotton, and
- the relationships that Monsanto developed with those key players in order to commercialise the Bt gene.

What is INGARD Cotton?

Cotton is naturally vulnerable to pests such as the cotton bollworm *(Helicoverpa armigera)* and the native budworm (*Helicoverpa punctigera*), commonly called heliothis pests. Managing these pests is a major problem for many cotton farmers. The bacterium *Bacillus thuringiensis* naturally produces a protein (Bt) which is toxic to these pest, and is itself used as a pesticide in organic farming.

INGARD cotton has been modified by the insertion of the Bt gene derived from *Bacillus thuringiensis* together with a promoter region into the cotton DNA. The genetically modified cotton plant expresses the Bt toxin. When these caterpillars eat the leaves of the modified cotton plant, the protein interrupts their digestion which causes them to stop feeding and die. The impact of the gene is very specific. It kills only the particular pest species and has no impact on natural predators such as spiders. It is also harmless to humans and other animals.

KEY DATES IN THE DEVELOPMENT OF THE INGARD BT TECHNOLOGY

1901: Humans first "discovered" Bt when Japanese bacteriologist Ishiwta Shigentane isolated some on a diseased silkworm, *Bombyx mori*, in Japan. Shigetane called Bt the *Sotto bacilus*, but this name did not last.

1915: German scientist Ernst Berliner isolated Bt from a dead Mediterranean flour moth, *Angasta kuehniella*, that he found in a grain mill in the German district of Thuringen. He named it, *Bacillus thuringiensis*. Berliner's name did last.

1927: The first Bt preparation targeting Lepidopteran insects was introduced in Germany. It was based on a Bt called *kurstaki*, sometimes called *berliner* after the scientist who named Bt.

1938: The first commercial Bt product, called Sporeine, was released in France.

1940s: With World War II came a surge in chemical advances, such as antibiotics and insecticides. Cheap and effective chemicals helped farmers solve many formerly unsolvable problems.

1957: The first large-scale Bt-based produce was sold by Sandoz Corporation. It was marketed as Thuricide, and was based on Bt *kurstaki*.

1966: USDA scientist Howard Dulmage jump-started the US Bt industry by isolating amore effective strain of Bt *kurstaki*. Named after Dulmage, "HD-a" quickly became the basis for many new Bt commercial products. It still is.

1977: Two scientists reported that, for the first time, a Bt variety, called *israelensis*, isolated in 1976, killed mosquito and black fly larvae; both are from the order Diptera (two-winged insects – mosquitoes and flies). This was the first documented case of a Bt strain killing an insect other than a caterpillar.

1981: Scientists Ernst Schnepf and Helen Whiteley were the first to clone (make an identical copy of) a Bt toxin gene. Soon after, these scientists sequenced (or chemically spelt out) that same gene. By 1989, more than 40 Bt genes were sequenced.

1985: Global sales of Bt insecticides exceeded $50 million, but remained less than 1% of the insecticide market.

1987: Three groups of scientists spliced Bt genes into cotton plants. None of the plants was commercially viable, but a brand new way to deliver Bt was created.

1988: A Monsanto scientist produced the first cotton plants with Bt toxin genes expressing their protein at potentially commercially viable levels.

1990: With United States Department of Agriculture approval, Monsanto began field tests of Bt cotton in the USA.

1992: With approval from the Genetic Manipulation Advisory Committee, field trials commenced in Australia.

1996: Approval for use in limited areas in Australia.

The application by Monsanto for commercialisation of INGARD cotton in Australia summarised the nature and effect of the genetic modification as follows:

> "The parent organism is cultivated cotton, *Gossypium hirsutum*. Cotton, which is exotic to Australia, is grown in Australia as a major agricultural crop. The transgenic plants have been modified to express a gene, derived from the bacterium *Bacillus thuringiensis*, that produces a highly specific insecticidal protein (Bt) that is toxic to the major caterpillar pests of cotton. Caterpillars are normally controlled by heavy spraying with pesticides. The Bt protein is non-toxic to humans, other animals and most other insects.
>
> "A delta-endotoxin gene has been inserted into the cotton to produce the CryIA(c) insecticidal protein. Transgenic plants express this gene in most plant parts, particularly in young leaves and flower buds. When the plants are attacked by insect pests which are susceptible to the toxins, the toxins initially inhibit insect feeding and subsequently result in the death of the insect pests. The target pests are two species of *Helicoverpa*, major pests in the cotton industry. In addition to the Bt-toxin genes, the transgenic cotton plants contain a selectable 'marker' gene, neomycin phosphotransferase, that confers resistance to the antibiotics kanamycin and neomycin.
>
> "This marker gene was inserted to allow selection of the transgenic plants from non-modified plants during regeneration of the plants in tissue culture. The inserted DNA also contains a bacterial gene, encoding resistance to spectinomycin and streptomycin, which is not expressed in the transgenic

> plants. This gene was used as a selectable marker for the genetic manipulations in the bacterial hosts, before the transfer of the gene to the cotton plants."

What IP Protection applies to INGARD cotton?

Three types of intellectual property have been used to protect INGARD® cotton:

- the Bt gene is protected by a patent
- the name INGARD is protected by a trade mark registration, and
- some new cotton varieties that use the Bt gene are protected by plant breeders' rights.

Each of these types of intellectual property is discussed below.

Patent protection for the Bt gene

Patents provide legal protection for inventions, including products or processes, that are new, involve an inventive step, and are capable of industrial application. *Module Two: Biotechnology and Intellectual Property* provides more details about the legal requirements for patenting. Patents are granted through national patent offices, such as IP Australia. The process requires the filing of a patent application that discloses how to work the invention. This is published by the patent office and examined by a patent examiner to ensure that it meets the legal requirements for patenting. If the patent meets the legal requirements of novelty, inventive step and industrial application, and there is no opposition, a patent is granted. More detail on the application process for patents is in *Module Three Reading a Biotechnology Patent and the Patent Process*.

The Bt gene in seed distributed by Monsanto is protected by Australian Patent Number 638 438. The patent provides for:

> a modified chimeric gene containing a promoter which functions in plant cells operably linked to a structural coding sequences and a 3' end wherein structural coding sequences encodes an insecticidal protein of *Bacillus thuringiensis*, wherein the naturally occurring DNA sequence of said structural coding sequence has been modified without changing the protein coded for by the sequence in a method comprising removing the occurrence of more than 5 consecutive adenine and thymine residues.

The patent describes the process for modifying existing genes or for creating totally synthetic genes by removing or modifying ATITA sequences that have prevented expression of the bacterial genes in plants through providing misleading gene control signals when expressed in the plant genome. These A-T rich sequences are modified by use of synthetic oligogonucleotides, which maintain the proper amino acid sequences while altering the underlying DNA, and while also bringing the A+T ratio towards 50% (typical of plants, but not Bt in its natural state.)

The 39 claims of the patent cover the inventive concept in different ways:

- claims 1-13 refer to modified chimera genes
- claims 14-26 refer to variation of claim 3 and related plant vectors
- claims 27-35 relate to methods for improving heterologous gene expression in plants through modification of the promoter sequence
- claim 36 extends the claims to plant cells
- claim 37 extends claims 36 to plant cells of soybean, cotton, alfalfa, oilseed, rape, flax, tomato, sugarbeet, sunflower, potato, tobacco, maize, rice and wheat
- claim 38 extends claims 36 and 37 to whole plants, and
- claim 39 extends claims 1-24 and 26 to seeds.

Despite the scope of this patent, several other firms have developed and patented their own Bt technology. These firms include Aventis CropScience, Marrion Merrel Dow and AgrEvo.

INGARD â Technology Users' Agreement

Monsanto's Bt-containing seed may only be used by growers who have a current Technology Users' Agreement with Monsanto Australia Ltd, which governs how the Bt technology has to be used, including such issues as resistance management. Any use of the ingard technology that contravenes the Agreement is subject to claims of patent infringement and/or breach of Agreement. A copy of the Technology Users' Agreement is at Attachment 3. Monsanto's development of such an agreement is a unique commercialisation strategy in the seed market to get a viable financial return on the R&D expenditure it spent developing the Bt gene.

The Technology Users' Agreement requires users to manage the technology, including applying a Resistance Management Plan, through::

- refuges: each grower is required to grow a refuge crop within the farm unit growing INGARD cotton
- planting window: all INGARD crops and cotton refuges must be planted and watered up within the period nominated in the Plan
- post harvest crop destruction: post-harvest crop destruction and removal of germinating volunteer cotton should be undertaken, as specified in the Plan
- pupae destruction: heliothis pupae must be destroyed by soil cultivation after harvest, as detailed in the Plan, and
- trap crops: each grower is required to plant a trap crop within the farm unit growing INGARD cotton.

The Technology Users' Agreement was developed in order to enable Monsanto to track how the crop is used and its impact on the environment. Monsanto must report on this to comply with the regulatory approvals it has. As such it must have a method of making sure that growers report the required data. Monsanto keeps this data confidential.

Trade mark protection for INGARD

A trade mark is a sign used to distinguish goods or services from the goods or services of another trader. A trade mark is infringed if a person uses, as a trade mark, a sign that is substantially identical to or deceptively similar to the registered trade mark. Trade marks do not need to be registered to get legal protection. However, registered trade marks are usually easier to enforce. Please see *Module One: Introduction to Intellectual Property* for more detail on trade marks.

The INGARD trade mark has been registered in Australia in two formats:

First, the trade mark is protected as the bare word 'INGARD.' This has been registered as trade mark number 658865, in respect of "genes for use in agriculture or horticulture, in particular, insect-tolerant genes for use in agricultural or horticultural seeds, and as trade mark number 658866 in respect of "genetically modified seeds, in particular, genetically modified agricultural or horticultural seeds which are insect-tolerant." This registration is subject to the endorsement that: It is a condition of registration that the word INGARD will not be used as the name, or part of the name, of a plant variety. These registrations are based on applications made in 1995.

Second, it is protected as a combination mark comprising the word INGARD and a stylized cotton logo together. This is registered under number 744265, based on an application made in 1997, in respect of:

- genes for use in agriculture or horticulture, including, insect-tolerant genes for use in agriculture or horticulture seeds being goods in this class
- cotton fabrics, piece goods of cotton and cotton blends; bed sheets; bed spreads; bed linen; table cloths; towels; blankets; handkerchiefs; all made wholly or in substantial part of cotton
- clothing, footwear and headgear
- agricultural products; cotton seed; unprocessed cotton seed oil; plant seeds; plants; seedlings; all the foregoing goods being goods included in this class

This registration is also subject to the endorsement that the word INGARD will not be used as the name, or part of the name, of a plant variety. This endorsement is aimed at ensuring that the trade mark owner cannot gain a continuing monopoly over the use of the common term used to designate a plant variety, given that the variety should be free for all to use once any plant breeder's rights have expired (see *Module Seven: Plant Breeder's Rights*).

This same product was commercialized in other countries using the trade mark BOLLGARD. It appears that it was originally not possible for Monsanto to use the BOLLGARD trade mark in Australia, because another company had already registered the trade mark BOLLGARD, under registration 608603 dating from 1993, in respect of pesticides, herbicides, fungicides and insecticides. In 1995, Monsanto applied for registration of the word trade mark BOLLGARD in respect of "genetic material for use in agriculture or horticulture, in particular, insect-tolerant genes or other such genetic material for use in agricultural or horticultural seeds; and all other goods in Class 1" (application 654595); and for "genetically modified seeds, in particular, genetically modified agricultural or horticultural seeds which are insect-tolerant; and all other goods in class 31" (application 654596). These applications were later withdrawn, possibly because of the conflict with the earlier registration 608603 of BOLLGARD in the name of the other company.

However, the other company's trade mark registration 608603 was cancelled in the year 2001 on the grounds that it had not been used. It is a general principle in trade mark law that a registration can be liable for removal or cancellation if the registered owner of the trade mark is not using it for the goods or services for which it has been registered. Once the registration has been cancelled, it opens up the possibility for others to use and register the trade mark. In fact, Monsanto has applied again for registration of BOLLGARD, and this application has very recently been approved for registration in Australia, presumably following the cancellation of the unused trade mark. This might clear the way for Monsanto to use the same trade mark in Australia as elsewhere.

To illustrate some of the issues associated with registering BOLLGARD as a trade mark, a decision of the European trade mark authority (OHIM) is provided at Attachment Four.

Plant breeders' rights protection for new varieties using the Bt gene

Plant breeders' rights are a separate type of intellectual property rights that give plant breeders the right to protect new varieties of plants. Under the Australian *Plant Breeder's Rights Act 1994*, a "plant" includes all fungi and algae but does not include bacteria, bacteroids, mycoplasmas, viruses, viroid and bacteriophages. The Act provides that a plant breeder's rights include the rights to:

- produce or reproduce the propagating material
- condition the propagating material for the purpose of propagation
- offer the propagating material for sale
- sell the propagating material

- import the propagating material
- export the propagating material, and
- stock the propagating material.

In order to get plant breeder's rights, a new variety must be **distinct** from other known varieties, the characteristics of the variety must be **uniform** and they must be **stable** of different seasons of planting. These requirements are called the "DUS" requirements. New varieties are examined to check that they comply with the DUS requirements. Please see *Module Six: Plant Breeders' Rights* for more information.

Plant breeders' rights do not apply to genes. Therefore the actual Bt gene is not protected by plant breeders' rights. Similarly, plant breeders' rights do not apply to bacteria – so a new strain of the *Bacillus thuringiensis* bacterium could not be protected by plant breeders rights. However, new plant varieties that contain the Bt gene can be protected by plant breeders' rights provided they meet the DUS criteria. As can be seen from the table below, out of 31 varieties of cotton (*Gossypium Hirsutum*) on the Plant Breeders' Rights database only five of these seem to be directly Bt related. All of these were registered in 1996.

Name of applicant	Number of Bt cotton varieties	Total number of cotton varieties
CSIRO Plant Industry	5	22
Delta Pine Australia Pty Ltd	0	5
D&P Technology Holding Corporation	0	2
Delta and Pine Land Company	0	1
Mrs Kamila Ullman and Professor VN Fursov	0	2

What Health and Safety Regulatory Frameworks Affect INGARD Cotton?

An important point to remember is that the grant of a patent or plant variety right does not give you a right to market your invention. Technology that is protected by IP rights is still subject to Government regulations, such as regulations on environmental protection, health and safety. Accordingly, even though Monsanto got patent protection for the Bt gene and trade mark protection for "INGARD®" it was unable to market INGARD® cotton until it had also got all the necessary Government regulatory approvals. Before Monsanto commercialised Bt cotton it needed to get regulatory approval from:

- the National Registration Authority
- the Genetic Manipulation Advisory Committee (GMAC), and
- the Australian and New Zealand Food Authority (ANZFA).

Each of these regulatory frameworks is discussed below. If any of these regulatory bodies had not approved the marketing of Bt cotton, Monsanto's patented invention, INGARD® cotton, would not have been able to be sold. For this reason it is very important to consider which regulatory frameworks are relevant to your invention during your research to make sure that you will comply with their requirements.

Registration of the Bt gene with the National Registration Authority

The INGARD gene is registered with the National Registration Authority for Agricultural and Veterinary Chemicals (NRA), under the Agricultural and Veterinary Chemicals Code. The NRA Approval No for INGARD is 48296/0997.

The NRA assesses all agricultural and veterinary chemicals before they can be marketed in Australia. The NRA requires full data packages on chemistry/stability, toxicology, residues, trade, metabolism, occupational health and safety, efficacy, crop safety, environmental fate and ecotoxicology before granting approval. New plant varieties are not normally required to be approved by the NRA, but INGARD cotton required registration because its leaves are a pesticide/insecticide.

In addition, the NRA requires ongoing reporting as a condition of registration. For example, Monsanto must detail product performance and grower compliance determined from industry audits, research and surveillance to ensure the continuing registration of INGARD with the NRA.

Fees are imposed by the NRA under the Agricultural and Veterinary Chemicals Act 1994, and vary depending on the complexity of an application. For example, a primary application taking 15 months to assess is charged at $20,620 whilst a new product similar to one already registered may take only 3 months to assess and is levied at $620. To continue registration, payment of registration renewal fees is required.

Genetic Manipulation Advisory Committee

The Genetic Manipulation Advisory Committee (GMAC), was a statutory body established by the Australian Government to:

- oversee the development and use of innovative genetic manipulation techniques in Australia so that any biosafety risk factors associated with the novel genetics of manipulated organisms are identified and can be managed; and
- to advise the Minister about matters affecting the regulation of innovative genetic manipulation technology.

The responsibilities of GMAC extended to all techniques that can transfer genetic material between species that may not normally exchange genetic material in natural circumstances, and to non-traditional techniques capable of modifying the genetic material of organisms. GMAC was concerned with risk factors associated with the altered genetic capabilities of a genetically modified organism (GMO), which may give rise to safety concerns in public health and safety, agricultural production, and the quality of the environment.

INGARD® cotton was approved by GMAC for use in limited areas in 1996. It needed to be approved by GMAC because of the transgenic nature of the modified cotton and the potential for environmental impact. As you can see from the table below, almost 90 cotton trials have been approved by GMAC since 1995.

Trial applicant	Number of trials	Years trials conducted
CSIRO Division of Plant Industry	45	1993-2001
Deltapine Australia	31	1993-2000
Cotton Seed Distributors	6	1998-2000

Agriculture Western Australia	2	1998-1999
CSIRO Division of Entomology	2	1998, 1999
Applied Horticultural Research	1	1997
Monsanto	1	1999-2000

Following the passage of a revised legislative framework for regulation of gene technology, the *Gene Technology Act 2000*, GMAC has been replaced by the office of the Gene Technology Regulator (OGTR), with responsibilities including approval of genetically modified organisms. The OGTR therefore has continuing responsibility for regulation of the use of the INGARD gene technology.

Australia and New Zealand Food Authority

The Australia and New Zealand Food Authority (ANZFA) is responsible for approval of genetically modified food in Australia and New Zealand. Bt cotton has been registered with ANZFA and approved for sale. This was necessary because one of its processed products, cotton seed oil, is used for human consumption.

ANZFA had issued guidelines for the safety assessment of foods to be produced using gene technology. ANZFA assessed the following safety issues:

- the direct consequences of new gene products in food encoded by genes introduced during genetic modification including physiochemical characteristics, allergenicity, impact on nutritional status,
- the direct consequences of altered levels of existing gene products encoded by genes introduced or modified during genetic modification
- the indirect consequences of the affect of any new gene or gene products including modification of the expression of another gene or modification of the metabolic pathways of other genes or their products
- the possibility of gene transfer from ingested genetically modified organisms and/or food or food components derived from them, including the potential consequences of transfer of an introduced gene into the micro-organisms into the human get, and
- the potential for adverse health effects associated with genetically modified micro-organisms including their ability to compete for nutrients and to alter intestinal flora in humans.

Who are the Key Players in INGARD Cotton?

Apart from gaining the necessary regulatory approval, it was also necessary to find appropriate technical, commercial and legal pathways to the commercialisation of the Bt gene technology in cotton. This meant that a complex relationship between various partners was necessary. The key players involved in the commercial development of INGARD cotton in Australia are.

- Monsanto: the owners of the Bt patent and the INGARD® trade mark
- CSIRO: the public sector research institution which owns variety rights on cotton germplasm
- Cotton R&D Corporation: the research funders, and
- Cotton Seed Distributors and Delta Pine: two commercial seed firms.

The role of each of these bodies is set out below.

Monsanto

Monsanto is a global life sciences company that makes and markets high-value agricultural products, pharmaceuticals and food ingredients. It has included insect resistance management as an integral part of its development of crops protected against insect pests. Monsanto believes that "resistance management is more than 'good citizenship'; it also preserves the value of products that have taken years to develop".

Monsanto researchers commenced work with *Bacillus thuringiensis* (Bt) in 1985. In 1989, scientists at Monsanto spliced the gene from Bt into cotton plants. Their research also enabled them to increase the expression of the gene one thousandfold. It was clear that the process had commercial potential as the greatly increased levels of the Bt toxin expressed in cotton plants with INGARD® killed caterpillars in greenhouse tests at levels equal to or better than leading insecticides.

Field tests began in the US in 1990. Australian varieties of INGARD were developed by importing a 'parental' line containing the gene from Monsanto USA into Australia in 1992. The gene was then crossed and backcrossed with the best Australian varieties, thus transferring the INGARD gene into CSIRO and Deltapine (DP) varieties.

In addition to INGARD cotton, Monsanto Australia Ltd is currently developing Roundup Ready® Cotton, INGARD cotton containing two Bt genes, and Roundup Ready® Canola for use by Australian farmers. Monsanto has applied to the Australian Government for permission to import products derived from genetically modified crops grown overseas. These include Roundup Ready soybean, Roundup Ready canola, Bt corn, Roundup Ready corn, Bt potato, and Bt potato with leaf roll virus.

Cotton Research and Development Corporation

The Australian Cotton Research and Development Corporation (CRDC) was established in 1990 under the *Primary Industries and Energy Research and Development Act* 1989. The role of the CRDC is to increase the contribution that R&D makes to the cotton industry and the community in general. The Corporation aims to achieve this goal by developing efficient, sustainable production systems, improving fibre quality to better meet market needs, and developing efficient handling, transport and marketing systems and infrastructure.

The primary functions of the CRDC include:

- investigating and evaluating the research and development requirements of the cotton industry
- preparing, reviewing and revising a research and development plan for the cotton industry
- monitoring, evaluating and reporting to Federal Parliament, the Minister for Primary Industries and Energy and ACGRA on research and development activities with which the CRDC is involved, and
- facilitating the dissemination, adoption and commercialisation of the results of cotton research and development (section 11 of the *Primary Industries and Energy Research and Development Act*).

The CRDC administers about 40% of all cotton R&D funding in Australia. Each year about $6m is allocated to over 100 projects addressing a wide range of issues associated with cotton production. Funds for projects administered by CRDC are from industry and the Australian Government. Growers contribute a levy of $1.75 per 227 bale which is matched by the government on a dollar for dollar basis up to 0.5% of the value of the industry's gross production of cotton lint. Income is also generated from a share of royalties on the seed sales of CSIRO-bred cotton varieties.

INGARD cotton is an important part of the CRDC's Integrated Pest Management plan. CRDC funded CSIRO for some of its research into the development of varieties using the INGARD technology. During the commercial and experimental trial stages for INGARD in Australia, the CRDC represented the views of local growers concerning licence fees for use of INGARD cotton in Australia.

CSIRO Division of Plant Industry

The Commonwealth Scientific and Industrial Research Organization (CSIRO) is the principal public sector research institution in Australia, with a wide range of activities and specific expertise in agronomy and plant biotechnology. Today, more than 90% of Australia's cotton is grown from seed developed by CSIRO. The Cotton Research Unit (CRU) at CSIRO has imported many hundreds of varieties from around the world and evaluated them in Australia for useful characteristics. These are incorporated into the cotton breeding programs at CSIRO to produce new plant varieties.

Varieties of cotton containing the Bt gene were developed by CSIRO and its commercial partners including Monsanto and Cotton Seed Distributors (CSD). The aim of the research was to develop cotton varieties with built in pest resistance to suit Australian conditions. Annual field trials of six transgenic varieties expressing the toxin gene began in the 1992/93 cotton season. The aims were to evaluate the effectiveness of the plants in killing larvae when grown under field conditions, and to commence studies of the impact of this cotton on other insects and the environment.

CSIRO has also collaborated with Cotton Seed Distributors (CSD), Monsanto and Rhone Poulenc, who are at the forefront of development technologies for new varieties.

Australian Cotton Cooperative Research Centre (CRC)

The Australian Cotton Cooperative Research Centre (CRC) commenced operations in 1997. The Cotton CRC is funded by the Australian Government. The organisation is located within the CSIRO's Cotton Research Institute at Narrabri in NSW. The purpose of the Cotton CRC is to enhance the development and growth of the Australian cotton industry through collaborative research, education and the adoption of sustainable farming systems which are environmentally responsible, increase the reliability of production and increase market competitiveness.

The Cotton CRC is a collaborative structure involving:

- CSIRO Division of Plant Industry, Division of Entomology, Division of Tropical Agriculture and Division of Textiles and Fibres
- NSW Department of Agriculture
- Queensland Department of Primary Industry
- Agriculture Western Australia
- Northern Territory Department of Primary Industry and Fisheries
- Cotton Research and Development Corporation
- Cotton Seed Distributors
- Queensland Cotton
- Western Agricultural Industries
- Twynam Cotton
- the University of New England, and
- the University of Sydney.

The CRC is an unincorporated joint venture hence agreements for R&D program are negotiated by the participants under the CRC umbrella, rather than by the CRC. There will be no legal agreements between companies such as Monsanto and the CRC itself.

Cotton Seed Distributors

Cotton Seed Distributors (CSD), is a grower-controlled organisation based in Wee Waa, New South Wales. It is Australia's largest supplier of commercial cotton seed. It has been developing new varieties of cotton since it was established in 1967.

During the 1998/99 season, Cotton Seed Distributors established a total of 52 variety trials, consisting of 32 conventional and 13 INGARD® trials, spread across all the cotton growing regions in Australia. These trials are undertaken by CSD agronomists, to ensure that the trials are

conducted in accordance with the Cotton Research and Development Corporation (CRDC) protocols. Members of the CSIRO cotton plant breeding team and CSIRO extension team also regularly monitor varietal performance in the trial during the season.

CSD and CSIRO have collaborated to provide cotton varieties with improved performance. Innovation has been a consuming focus of the collaboration, which has seen the development of many cotton varieties of value to both the grower and value-added industries of spinning and yarn manufacture, aiming at making a substantial contribution to the cotton industry.

Deltapine Pty Ltd

The Delta & Pine Land Company (Deltapine), operates the oldest, continuous private cotton breeding program in the US. The company became US owned in 1978 after a British conglomerate sold its interests to US investors. Deltapine became a publicly listed company on the NASDAQ Exchange in 1993. In 1995 it moved its listing onto the New York Stock Exchange [DPL].

The company is involved in the breeding of conventional and new transgenic cotton and soybean varieties. It controls 56 test locations across America. The company also controls 4000 conventional varieties in yield tests and 1,400 transgenic lines in yield trials. Deltapine's product list includes conventional varieties of cotton planting seed as well as transgenic varieties.

Deltapine was the first company to introduce transgenic cotton seed featuring the Bollgard or Bt gene technology under licence from Monsanto.

What was the process of commercialising INGARD cotton?

Monsanto developed commercial relationships with a range of different parties in the process of commercialising INGARD cotton. This is an important practical point. The commercialisation process often requires you to build relationships with other people. This is the case whether you are a backyard inventor or part of a multinational corporation. You need assistance from other people because you might not have all the technology, skills, time or financial resources to commercialise your invention alone.

Despite spending many years researching and developing the Bt gene and its expression in plant systems, and gaining patents on its research outcomes, Monsanto did not have access to suitable germplasm necessary to develop new varieties of cotton bearing the gene for production in Australia. It therefore needed to find partners with whom it could develop new varieties for sale to commercial growers. Figure 1 sets out the relationships that enabled commercialisation of cotton in Australia with the INGARD gene technology.

Monsanto's relationship with CSIRO

As noted above, Monsanto developed the Bt technology. However, it did not have the germ plasm required to develop new varieties of plant and therefore seed.

The Australian CSIRO was aware of Monsanto's work in the US developing new cotton varieties and approached Monsanto about collaboration. CSIRO held the germ plasm which could them be combined with the Bt gene to develop varieties suited to Australian conditions. In Australia, CSIRO is Monsanto's main research partner. It has R&D contracts with Monsanto to undertake research using the BT gene and promoter sequences.

CSIRO needed to negotiate a separate arrangement with Monsanto to be in a position to commercialise the R&D through its business partner, Cotton Seed Distributors. In theory, the technology holder could refuse to extend the license for commercial purposes – there may be concerns about product liability or such issues as resistance management. In other cases in Australia, research institutes have secured a license to use technology for research, but have been refused extensions of the license for commercial use. CSIRO now includes in its research planning consideration of the route to market for proposed research outcomes, including protection of the IP it generates and strategies for negotiating

CSIRO's relationship with its funding body

CSD pays a royalty to CSIRO for developing the varieties for commercial release. As the Cotton R&D Corporation has funded some of the CSIRO's research into using Bt in Australian cotton varieties, CSIRO also pays a royalty back to CRDC for this support.

Monsanto's relationships with commercial seed distributors

Usually, the seed market is high volume and low profit – similar to most commodity markets. Thus despite spending many years researching and developing the Bt gene and its expression in plant systems, it would have been difficult for Monsanto to have launched its own seed variety to sell into a market which was used to paying low prices for seed. This is why Monsanto developed the concept of combining payment for the seed with licences for the technology itself.

Cotton Seed Distributors and Deltapine are major commercial seed distributors and as shown in the diagram above they both have a licence from Monsanto to use the Bt gene promoter in cotton varieties.

Cotton Seed Distributors has two licences. It has an exclusive licence from CSIRO for its cotton varieties and a separate licence from Monsanto to use the Bt gene promoter contained in these varieties. Deltapine imports cotton varieties from overseas and has a local breeding program to develop varieties suitable for the Australian market so it does not need a licence from CSIRO for cotton varieties. However, Deltapine does have a licence from Monsanto to use the Bt gene promoter contained in the Bt cotton varieties that it breeds.

Monsanto's relationship with growers

The growers purchase the cotton seed direct from either Deltapine or Cotton Seed Distributors. However, they also must sign a Technology User Agreement and provide a payment direct to Monsanto that is designed to reimburse Monsanto for its R&D in developing gene technology. The Technology User Agreement also binds the growers to collect data for Monsanto's use in its reports to the regulatory agencies that control commercialisation of genetically modified plants.

Costs of research, breeding and regulatory approvals

In any commercial decisions by companies like Monsanto, the cost of breeding programs and the regulatory process needs to be taken into account in addition to the cost of the research. In addition to the approximately $100 million that Monsanto has spent on its R&D, it costs a further $5 million to develop breeding programs for any new varieties and an equivalent amount of the product development pathway and regulatory requirements. Thus the size of the crop grown in Australia, or any other country is likely to affect a business decision by a large corporation regarding release this or similar gene technology. Regulatory fees are the same for every release of a new plant variety, whether or not a similar technology has been released before. Thus even though Bt cotton is approved for release in Australia, developers of any other variety would have to go through the same processes with the Office of the Gene Technology Regulator to have another crop with Bt genes approved for commercial use.

Field performance of INGARD cotton

Since the commercial release of INGARD® was approved in 1996 the field performance of INGARD cotton has been extensively reviewed. The performance of INGARD has not been as expected by CSIRO, Monsanto and the cotton industry, although it has provided benefits to the cotton grower and the community through the use of reduced insecticides. According to one official report:

> GM crops have the potential to reduce the need for toxic chemical sprays. In Australia in the 1998/1999 season, INGARD® (insect-resistant) cotton (the only GM crop currently released commercially in Australia) required 44% fewer pesticide sprays than conventional cotton.

Some aspects of this case study

This section provides a brief overview of a very complex process and set of relationships. Some distinctive features of this case study are:

- Licensing of the INGARD gene technology to cotton growers through the Technology User Agreement, separately from the sale of seed, and the creation of a distinct royalty stream reflecting the value of the technology as such apart from the underlying cotton seed;
- The overlap between public and private sector activities, and the need for commercial relationships to provide support both for the cost of research and development and for the regulatory approval processes such as field tests and toxicity tests required before release to growers;
- The need for research organizations to consider the longer-term needs of commercialisation, and freedom to operate in making their new technologies available for general use, apart from negotiation of agreements for use of technology in research and development;
- The relationship between licensing of IP rights and the legal mechanism of a contract between technology provider and technology user, on the one hand, and a program of technology management including monitoring use to check compliance with environmental regulations and managing resistance, on the other hand;
- The need for the technology developer (the Bt gene and promoter) to cross-license or otherwise get access to platform technologies which are necessary for the successful application of the new technology;
- The practical implications of freedom to operate considerations and IP management for those funding and undertaking research, including public sector institutions, and
- .The need for public sector researchers and funding agencies to manage the costs of regulatory approval, particularly for products which are for smaller or more specialised applications where private sector players are unlikely, for commercial reasons, to cover compliance costs and bear other risks.

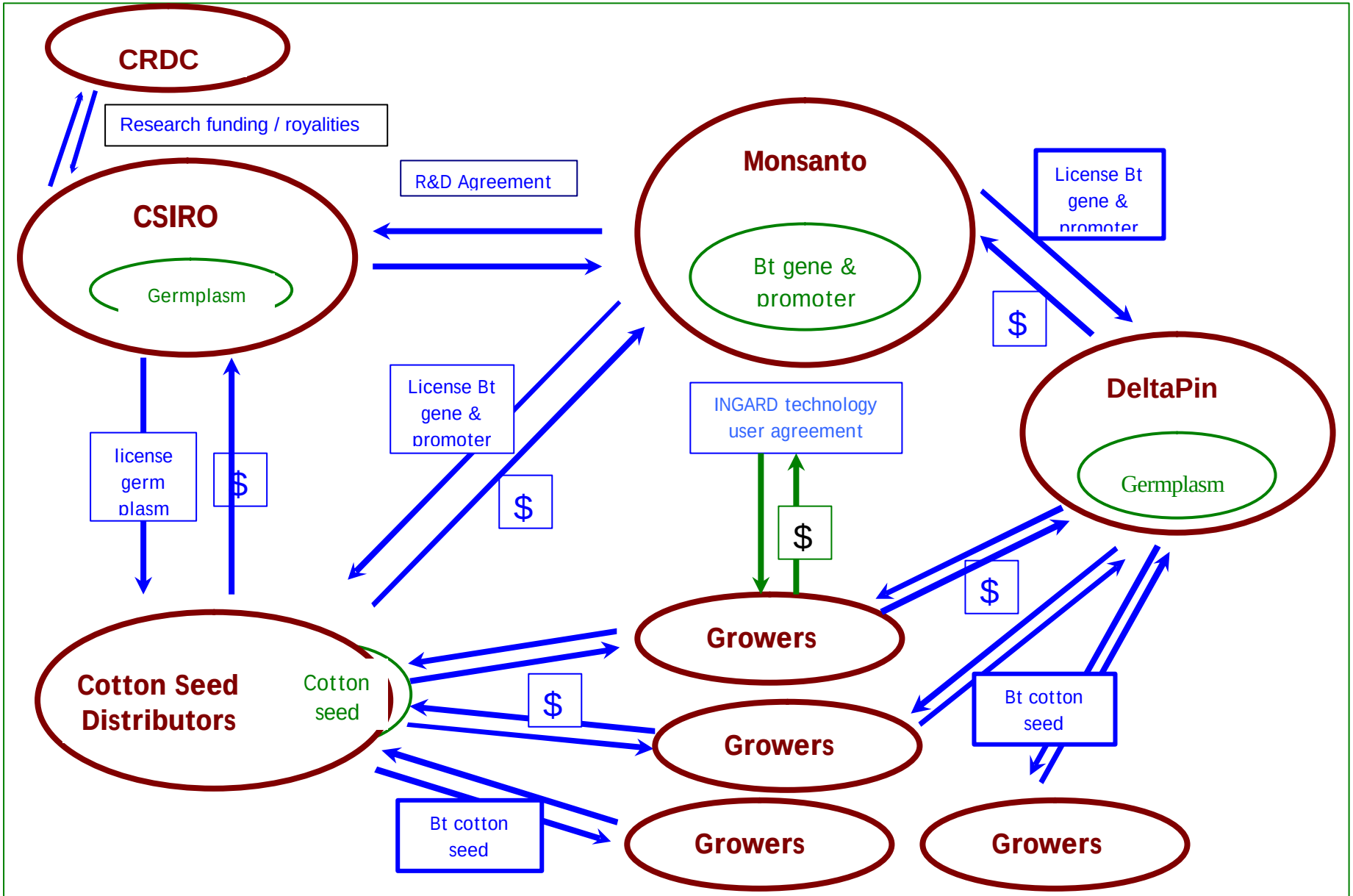


Figure 1: Relationships in Bt

10.5 Group Exercises on "Bt Cotton" Case Study

Please discuss the Bt Cotton case study with your fellow participants and prepare answers to the following questions.

Exercise 10.5.1 - patents compared with plant breeders' rights

Monsanto got patent protection for the Bt gene. Why couldn't Monsanto get plant breeders' rights protection for the Bt gene or for plant varieties including Bt cotton?

Exercise 10.5.2 - Monsanto's licence arrangements for use of the Bt gene

Why do you think that Monsanto licenses use of the Bt gene, rather than commercialising the invention on its own?

Exercise 10.5.3 - building relationships in commercialising an invention

Why did Monsanto and CSIRO develop a commercial relationship in the development of Bt cotton? What did Monsanto need from CSIRO?

Exercise 10.5.4 - regulatory approvals for Bt cotton

(i) What regulatory approvals did Monsanto need to commercialise Bt cotton?

(ii) Imagine that Monsanto had failed to get regulatory approval to market Bt cotton. If this had happened, do you think that Monsanto could have marketed Bt cotton anyway because it had a patent? Why?

Exercise 10.5.5 - Monsanto's Technology Users' Agreement

Why did Monsanto develop the Technology Users' Agreement? What are its purposes?

Exercise 10.5.6 - Bt cotton and CSIRO

What do you think are some advantages and disadvantages for CSIRO from the way in which Monsanto has commercialised the Bt gene?

Exercise 10.5.7 - Bt cotton and Cotton Seed Distributors

What do you think are some advantages and disadvantages for Cotton Seed Distributors from the way in which Monsanto has commercialised the Bt gene?

Exercise 10.5.8 - Bt cotton trade marks

(i) What trade marks have been used in relation to Bt cotton? Why did Monsanto use a different trade mark in Australia and in other countries? What legal options were open to it to bring its Australian mark into line with the other countries?

(ii) What goods were covered in the registration of the INGARD logo? What does this suggest about the possible commercialisation of this invention?

10.6 Summary of Module Ten

Commercialising your invention is a way to get possible financial benefits from your work. The Eternal® Papayas and Bt Cotton Case Studies show you how it can be done. The checklist below sets out key steps for commercialising an invention. Other Modules give details about these steps:

Module One: Introduction to Intellectual Property Law gives an overview of the types of intellectual property.

Module Two: Biotechnology and Intellectual Property sets out the legal requirements for getting a patent.

Module Three: Reading a Biotechnology Patent and the Patent Process sets out the administrative steps to get a patent.

Module Four: Searching Patent Databases sets out how to track down technical information to help your research.

Module Five: Group Exercise on Patent Validity: Neem gives you practical experience in reading and analysing a patent.

Module Six: Group Exercise on Patent Validity: Relaxin provides similar experience in relation to a more complex pharmaceutical patent involving DNA-related claims and ethical issues.

Module Seven: Plant Breeders' Rights sets out details about plant breeders' rights.

Module Eight: Researching and Intellectual Property Rights sets out how to develop a R&D and IP strategy, get freedom to operate, and negotiate contracts with commercial partners.

Module Nine: Licensing and Enforcing Intellectual Property Rights tells you how to make the most of your intellectual property by exploiting and protecting it.

This Module brings it all together.

Commercialisation Checklist

How to Take Your Invention from the Laboratory to the Marketplace

✓ **Develop a combined R&D and IP strategy** at the start of your research to make sure that you will be able to get IP rights and benefit from commercialising your invention if your research is successful, e.g. keep your invention secret until you apply for a patent!

✓ **Do a patent survey** to see what research has already been done and what existing IP rights might affect the use of your research outcome.

✓ **Create a new invention**!

✓ **Get intellectual property protection** for your invention, such as a patent or plant breeders' rights

✓ **Keep a track of the costs of your invention** to help you decide whether or not to commercialise it and help you to work out a price for it if you do

✓ **Do business research before commercialisation** to check demand for your invention, to find out health and safety regulatory requirements in the countries you want to market your invention, and to check out commercial partners who might want to licence or buy your invention

✓ **Decide which model of commercialisation is best for you** such as licensing, assignment or joint venture

✓ **Establish "freedom to operate"** to make sure that commercialising your invention will not infringe someone else's patent rights

✓ **Enforce your valuable intellectual property rights**

✓ **Get expert advice** when you need it.

10.7 Attachments

Attachment 1: **Patent Rights Potentially Relevant to 'Papaya' Technology**

Attachment 2: **Relevant Patent Claims for Eternal â Papayas**

Attachment 3: **INGARD â Technology User Agreement 1999/2000**

Attachment 4: **OHIM decision on the BOLLGARD trade mark**

*Attachment 1: Patent Rights Potentially Relevant to "Papaya" Technology**

Technology	Assignee	PCT	Australia	Malaysia	USA	Europe	Others[1]	~ Expiry
Ripening-related ACS gene								
ACC Synthase genes	US Dept of Ag	WO92/04456	AU-B-85994/91	no filing	5,723,766 5,923,766	0 548 164 A4	MX; CA; JP	2012 Mar 2105 (USA
ACS from papaya	University of Qld	WO97/11166	AU-A-69200/96	PI 9603895	Allowed	pending	TA: 033348	Sept 2016
ACS from papaya	University of Hawaii				5,767,376			
Selectable marker gene								
nptII gene	Monsanto	WO84/02913	no separate filing; included in AU-B-24363/84	no filing	5,034,322	0 131 623 B2 (same as for 35S) Opposition Decision appears to be in appeal	JP	Jan. 2004 July 2008 (USA
Promoters								
maize ubiquitin I promoter	Mycogen (Dow AgroSciences)		no filing	?? check	5,510,474 5,614,399	0 342 926 B1 appears to have lapsed in AT; SE; C	CA; JP	May 2009 Aug. 2014 (US June 2015 (USA
nopaline synthase promoter	Monsanto		no filing	no filing	5,034,322	0 131 623 B2 Opposition Decision appears to be in appeal	JP	Jan. 2004 July 2008 (USA
CaMV35S promoter	Monsanto		no filing	no filing	5,352,605 5,530,196 5,858,742	0 131 623 B2 (same as for nptII) Opposition Decision appears to be in appeal	JP	Jan. 2004 Oct. 2011 (USA

Technology	Assignee	PCT	Australia	Malaysia	USA	Europe	Others[1]	~ Expiry
Transformation								
Biolistics	DuPont de Nemours BioRad (for the apparatus, *per se*)		no filing	no filing	4,945,050 5,036,006 5,100,792 5,371,015	no filing	CA	Nov. 2005 (CA July 2007 (USA July 2008 (USA Dec. 2011 (US
Binary Vector System	MOGEN		no filing	no filing	4,940,838 5,464,763	0 120 516 B1 0 159 418 B1	JP	Feb. 2004 July 2007 (USA
Agrobacterium-mediated	Max-Planck-Institute		AU-B-23274/84 (546542)	no filing	in interference proceedings before the US PTO	0 116 718 B2 0 290 799 A3 0 320 500 A3 status unclear; both seem to be pending	JP; IL JP JP	Jan. 2004 unknown (USA
Agrobacterium-mediated	Monsanto		AU-B-24363/84 (559562)	no filing	in interference	0 131 620 B1 (method/seed) 0 131 624 B1 (plasmids)	JP	Jan. 2004 unknown (USA
Down-regulation								
antisense	Calgene (Monsanto)		AU-B-70597/87 AU-A-13017/92 AU-A-44470/93 both lapsed	no filing	5,107,065 5,453,566 5,759,829	0 240 208 B1 seems to be in opposition 0 485 367 A1	CN; IL; JP; NZ	Mar. 2007 Apr. 2009 (USA Jan. 2006 (USA Apr. 2009 (USA
co-suppression (Transwitch)	DNA Plant Technology Corp.		AU-B-54123/90	no filing	5,034,323 5,231,020 5,283,184	0 465 572 B1 0 647 715 A1 (status not checked)	JP	Mar. 2010 July 2008 (USA July 2010 (USA July 2010 (USA
double hybrid	CSIRO	WO99/53050						

[1] CA = Canada; JP = Japan; MX = Mexico; TA = Thailand; CN = China; IL = Israel; NZ = New Zealand

Attachment 2: Relevant Patent Claims for Eternal â Papayas

BVS patent claims: US 4,940,838

1. A process for the incorporation of foreign DNA into chromosomes of dicotyledonous plants, comprising infecting the plants or incubating plant protoplasts with Agrobacterium bacteria, which contain plasmids, said Agrobacterium bacteria containing at least one plasmid having the vir-region of a Ti plasmid but no T-region, and at least one other plasmid having a T-region with incorporated therein foreign DNA, but no vir region.

BVS patent claims: EP 0 120 516

1. A process for the incorporation of foreign DNA into chromosomes of dicotyledonous plants, comprising infecting the plants or incubating plant protoplasts with Agrobacterium bacteria, which contain plasmids, said Agrobacterium bacteria containing at least one plasmid having the vir-region of a Ti plasmid but no T-region, and at least one other plasmid having an artificial T-region with only foreign DNA between the 23 base pairs at the extremeties of the wild type T-region, but no vir-region, the vir-region plasmid and the T-region plasmid containing no homology which could lead to co-integrate formation.

BVS patent claims: EP 0 159 418

1. A process for the incorporation of foreign DNA into the genome of monocotyledonous plants, by infecting the monocotyledonous plants or incubating the protoplasts thereof with Agrobacterium or Rhizobium bacteria containing a virulence region and at least one T-region originating from a Ti plasmid or a Ri plasmid or both, which T-region is provided with said foreign DNA.

nos-nptII patent claims: US 5,034,322

1. A chimaeric gene capable of expressing a polypeptide in a plant comprising in sequence:

   (a) a promoter region from a gene selected from the group consisting of an Agrobacterium tumefaciens opine synthase gene and a ribulose-1,5-bis-phosphate carboxylase small sub-unit gene;

   (b) a structural DNA sequence encoding a polypeptide that permits the selection of transformed plant cells containing said chimaeric gene by rendering said plant cells resistant to an amount of an antibiotic that would be toxic to non-transformed plant cells, said structural gene sequence being heterologous with respect to the promoter region; and

   (c) a 3' non-translated region of a gene naturally expressed in plants, said region encoding a signal sequence for polyadenylation of mRNA.

nos-nptII patent claims: US 5,034,322

2. A gene of claim 1 in which the polypeptide renders transformed plant cells resistant to an amount of an aminoglycoside antibiotic that would be toxic to non-transformed plant cells.

3. A gene of claim 2 in which the polypeptide is a neomycin phospho-transferase.

4. A gene of claim 1 in which the 3' non-translated region is selected from a gene from the group consisting of the genes from the T-DNA region of Agrobacterium tumefaciens.

5. A gene of claim 1 in which the 3' non-translated region is from the nopaline synthase gene of Agrobacterium tumefaciens.

CaMV35S patent claims: US 5,352,605

1. A chimaeric gene which is expressed in plant cells comprising a promoter from a cauliflower mosaic virus, said promoter selected from the group consisting of a CaMV (35S) promoter isolated from CaMV protein-encoding DNA sequences, and a structural sequence which is heterologous with respect to the promoter.

2. A chimaeric gene of claim 1 in which the promoter is the CaMV (35S) promoter.

3. A chimaeric gene of claim 1 in which the promoter is the CaMV (19S) promoter.

nos-nptII patent claims: EP 0 131 623

1. A chimaeric gene capable of expressing a polypeptide in plant cells comprising in sequence:

   (a) a promoter region from a gene which is naturally expressed in plant cells

   (b) a 5' non-translated region

   (c) a structural coding sequence encoding a neomycin phosphotransferase polypeptide; and

   (d) a 3' non-translated region of a gene naturally expressed in plant cells, said region encoding a signal sequence for polyadenylation of mRNA; said promoter being heterologous with respect to the structural coding sequence.

2. A gene of claim 1 in which the promoter is selected from a gene of the group consisting of a nopaline synthase gene and a ribulose-1,5-bis-phosphate carboxylase small sub-unit gene.

3. A gene of claim 1 in which the 3' non-translated region is selected from a gene from the group consisting of the genes from the T-DNA region of Agrobacterium tumefaciens.

4. A gene of claim 1 or 2 in which the 3' non-translated region is from the nopaline synthase gene of Agrobacterium tumefaciens.

During the Opposition Proceedings on EP 0 131 623, Claims 5-9 were deleted from the patent. Claims 5-9 were:

5. A chimaeric gene capable of expressing a polypeptide in plant cells comprising in sequence:

   (a) a promoter region from a plant virus;

   (b) a 5' non-translated region;

   (c) a structural coding sequence;

   (d) a 3' non-translated region of a gene naturally expressed in plants, said region encoding a signal sequence for polyadenylation of mRNA, said structural coding sequence being heterologous with respect to said promoter region.

6. A gene of claim 5 in which the promoter is from cauliflower mosaic virus.

7. A gene of claim 6 in which the 3' non-translated region is from a nopaline synthase gene.

8. A gene of claim 5 in which the promoter is the full-length transcript promoter of cauliflower mosaic virus.

9. A culture of micro-organisms identified by the ATCC accession number 39265.

Attachment 3: INGARD â Technology User Agreement 1999/2000

THE PARTIES AGREE:

1 APPOINTMENT AS AN INGARD TECHNOLOGY USER

1.1 Subject to the terms and conditions of this Agreement, Monsanto hereby grants to the INGARD Technology User, and the INGARD Technology User accepts, a non-exclusive license (the "License") to exploit patent no. 638 438 and to purchase and use the INGARD Gene Technology (the "Gene Technology") on he farm unit nominated on the Grower Information Details sheet on Schedule 1 of this Agreement (the "Farm Unit" and "Grower Information Details Sheet" respectively) to grow one single cotton crop during the 1999/2000 growing season

1.2 The Licence is restricted to use by the INGARD Technology User and may not be assigned to or exercise by any other person, firm or corporation other than the INGARD Technology User.

1.3 The INGARD Technology User is not licensed to use cotton seed varieties containing the INGARD gene (the "INGARD Cotton Seed") other than on the conditions set out in this Agreement

2. OBLIGATIONS OF INGARD TECHNOLOGY USER

2.1 During the term of this Agreement, the INGARD Technology User agrees that in consideration of the license it must:

(a) upon execution of this Agreement:

(i) complete the Grower Information details Sheet; and

(ii) provide a scaled map of the Farm Unit (showing surveyed fields) to the Technology service Provider nominated on the Grower Information details Sheet (the "Nominated TSP");

(b) before ordering INGARD Cotton Seed from a cotton seed supplier, obtain a Purchase Authority from the Nominated TSP. The Nominated TSP may be unable to issue a Purchase Authority in respect of the entire required amount of INGARD Cotton Seed due to limitations on the total hectares available for the 1999/2000 season imposed by the regulatory authorities;

(c) when applying for a Purchase Authority from the Nominated TSP, clearly indicate on the map referred to in clause 2.1(a)(11):

(i) the field intended to be planted with INGARD Cotton seed (together with the intended seeding rate and variety or varieties to be used); and

(ii) the type, size and location of the insect refuge required pursuant to the Resistance Management Plan for INGARD Cotton;

(d) not resell or supply any INGARD Cotton Seed to any other party;

(e) use INGARD Cotton Seed to plant only one crop for one growing season on the Farm Unit on an area which shall be greater than (or equal to) 20 hectares but less than (or equal to) 500 hectares or 25% of the Farm Uni (whichever is greater);

(f) strictly comply with the label directions and ensure that the INGARD Technology Uer's consultants and contractors do likewise;

(g) not save the seed produced from INGARD Cotton Seed for the purpose of use in cotton production nor sell any INGARD Cotton Seed (including the seed produced from INGARD Cotton) to anyone whom the INGARD Technology User knows or ought reasonable know intends or is likely to use or on-sell the INGARD Cotton Seed for the purposed of cotton production (the INGARD Technology User may, however, use tor sell the seed produced from INGARD Cotton Seed where the INGARD Technology Suer bona fide believes the purchaser intends to use it as stock feed or for cotton seed oil production);

(h) strictly follow the Resistance Management Plan for INGARD cotton;

(i) allow Monsanto or the Nominated TSP reasonable access to review crop management records and to inspect and test any INGARD Cotton Seed located on the Farm Unit for the purposes of:

(i) assisting the INGARD Technology User to implement the Resistance Management plant for INGARD Cotton;
(ii) and ensuring compliance with this Agreement;

(j) perform audits of the Farm Unit in the manner and at the times specified by Monsanto from time to time;
(k) notify Monsanto of any change in the size of the Farm Unit or any other details
(l) comply with all Federal, state and local laws, ordinances, rules, regulations, by-laws and policies applicable to the INGARD Technology User's performance of its obligations under this Agreement and all reasonable directions and instructions given by Monsanto.

If the INGARD Technology User ceases to purchase INGARD protection, the rights to inspect and test any INGARD Cotton or INGARD Cotton Seeds will continue for a period of three years after the last year in which the INGARD Technology User planted INGARD Cotton Seed.

3. ADDITIONAL INFORMATION

3.1 The INGARD Technology Use acknowledges that when growing INGARD Cotton:

(a) the control of Helicoverpa armigera and H. punctigera provided by INGARD Cotton may vary and require supplemental treatment by t the INTGARD Technology User in order to avoid economic damage;

(b) such variation can occur even in circumstances where the INGARD Technology User has complied with Clause 2(f).

4. INTELLECTUAL PROPERTY RIGHTS

4.1 The INGARD Technology User acknowledges tat nay and all trade marks, copyrights, patents and any other industrial or intellectual property rights whether arising by reason of statute or at common law or in equity ("Monsanto Rights") (including without limitation unpatented production methods and technical and confidential information so long as they are not public knowledge) embodied in or used in connection with the INGARD Gene Technology or communicated pursuant to this Agreement, are and remain the sole property of Monsanto.

4.2 The INGARD Technology User must report immediately to Monsanto any apparent infringements of Monsanto's Rights by third parties which come to the notice of the INAARD Technology User. The INGARD Technology User agrees that it will cooperate in the conduct of any action brought by Monsanto.

4.3 The INGARD Technology User must promptly disclose to Monsanto any improvement or development it may discover or devise in relation tot he INGARD Gene Technology and allow Monsanto to use, license or assign, without charge or restriction, any such improvement or development.

5. CONFIDENTIALITY OF MONSANTO INFORMATION

5.1 Monsanto will provide to the INGARD Technology User such information as is reasonably necessary for the purpose of the INGARD Technology User's compliance with government requirements in relation to this Agreement.

5.2 Any information which is communicated to the INGARD Technology User pursuant to clause 5.1 or any other information confidential to Monsanto otherwise communicated under this Agreement (individually and collectively referred to as the "Information") must be treated by the INGARD Technology User as confidential and must not be disclosed to any other person or corporation. This provision will not apply to the extent that:

(a) the INGARD Technology User has the written consent of Monsanto to disclose the Information; or

(b) the Information is or has been otherwise legally acquired by the INGARD Technology User from a third party (other than an INGARD Technology Service Provider) not in breach of any confidentiality obligation to Monsanto; or

(c) the Information is or comes into pubic domain or is or becomes generally known in the industry otherwise than by breach of this Agreement; or

(d) it is reasonably necessary for the INGARD Technology User to disclose their Information to its officers, directors and employees to enable those officers, directors and employees to perform their obligations in connection with the exercise of rights conferred by the License where those obligations are not inconsistent with the terms of this Agreement provided that the INGARD Technology User uses all reasonable endeavours to impose undertakings of confidentiality on those officers, directors, and employees to whom the Information was disclosed.

(e) The Information is required by any government instrumentality

If the INGARD Technology User is required to disclose the Information to a government instrumentality, all reasonable endeavours must be used by the INGARD Technology User to make disclosure under conditions of confidence.

5.3 The confidentiality obligations in cluse 5.2 will survive the termination of this Agreement

6. FARM UNIT INFORMATION

6.1 Monsanto will not reveal nay of the information acquired about he INGARD Technology User's Farm Unit as the result of this Agreement to any third parties except to the extent that Monsanto considers it necessary to disclose such information in order to:

(a) fulfil regulatory requirements;

(b) ensure compliance with this Agreement; or

(c) assist Cotton Seed Distributors Ltd. And DeltaPine Australia Pty. Ltd. To anticipate INGARD Cotton Seed demand

The information provided under this Agreement may be stored by Monsanto for a period of up to five years.

7. INGARD TECHNOLOGY USER'S LICENSE FEE

7.1 In consideration of the grant of the license, the INGARD Technology User hereby agrees to pay the Nominated TSP a fee (the 'License Fee")

7.2 In relation to each Farm Unit, the license Fee is A$185.00 per hectare of INGARD protection purchased by the INGARD Technology User pursuant to a Purchase Authority obtained in accordance with Clause 2.1(b)

7.3 The INGARD Technology User will be invoiced for the license Fee by the Nominate TSP on or about 14 December 1999.

7.4 Payment of the License Fee must be made by the INGARD Technology User to the Nominated TSP on or before 31 January 2000.

7.5 The INGARD Technology User acknowledges that should the INGARD Technology User fail to pay the license Fee in accordance with Clause 7.4, any and all Monsanto's rights to enforce the INGARD Technology User's obligations to pay may be enforced by the Nominated TSP as agent for Monsanto.

8. TERM

The term of this Agreement is for the period commencing on June 1, 1999 and ending on August 31, 2000 or when terminated by either party in accordance with clause 9 of this Agreement, whichever occurs first.

9. TERMINATION

9.1 If either party breaches any of the provisions of this Agreement, the other party may give notice to the first party of intent to terminate this Agreement specifying the alleged breach, and if the first party does not rectify that breach within 30 days after the service of that notice, the other party may terminate this Agreement forthwith by written notice to the first party.

9.2 Without limiting the generality of clause9, the Agreement and all rights granted herein, will terminate on written notice from Monsanto to the INGARD Technology User in the event that:

(a) any approval necessary for the due operation of this Agreement should be withdrawn; or

(b) effective control, by any means, of the INGARD Technology User is transferred to a person or corporation who does not have that control at the date of execution of this Agreement.

10. RIGHTS, DUTIES AND LIABILITIES UPON TERMINATION

10.1 Upon the termination of this Agreement, however caused, all rights and privileges of the INGARD Technology User under this Agreement will terminate.

10.2 Termination of this Agreement will have no effect by any means whatsoever upon any rights or liabilities which may arise from damages deriving from a breach of this Agreement prior to termination.

11. ASSIGNMENT

The INGARD Technology User may not assign any of its rights and/or liabilities pursuant to this Agreement without the prior written consent of Monsanto.

12. MISCELLANEOUS

12.1 This Agreement is governed by the laws in force in, and the parties submit to the non-exclusive jurisdiction of the courts of, the State of Victoria.

12.2 Any provision of this Agreement which is invalid or unenforceable in any jurisdiction will be ineffective in that jurisdiction to the extent only of such invalidity or unenforceability and will be severed from and will not invalidate the remaining provisions of this Agreement

12.3 The INGARD Technology User agrees that no failure or delay by Monsanto in exercising any right, power or privilege under this Agreement will operate as a wive thereof and no single or partial exercise thereof will preclude the exercise by Monsanto of any other right, power or privilege under this Agreement.

12.4 This Agreement may not be modified, amended or otherwise varied except by a document in writing signed by each of Monsanto and the INGARD Technology User (or an authorized representative thereof).

This Agreement supersedes all and any previous agreements whether oral or written in respect of the INGARD Gene Technology between the INGARD Technology User and Monsanto and any statement, disclosure, representation, warranty, condition, promise, undertaking or other provision not expressly set out in this Agreement has not been relied on and has no force or effect.

Attachment 4: OHIM Decision on the BOLLGARD trade mark

OFFICE FOR HARMONIZATION IN THE INTERNAL MARKET (TRADE MARKS & DESIGNS)

DECISION of the Third Board of Appeal of 21 October 1999 In Case R 266/1999-3

Monsanto Company
800 North Lindbergh Boulevard, St. Louis Missouri, USA
Applicant and Appellant

Ladas & Parry
52-54 High Holborn, London WC1V 6RR, United Kingdom
Representative

APPEAL relating to Community trade mark application number 549576

THE THIRD BOARD OF APPEAL
composed of S. Sandri (Chairman), Th. Margellos (Rapporteur) and A. Bender
Registrar: L. McGarry

gives the following **Decision**

Summary of the facts

1. By application filed on 2 June 1997 the applicant sought to register the word mark **BOLLGARD** for 'Insect-tolerant genes for use in agricultural seeds' in Class 1, 'Agricultural seeds containing insect-tolerant genes' in Class 31 and 'Cotton' in Class 22.

2. In a notice by fax of 3 December 1998, the examiner informed the applicant that the claimed trade mark did not appear to be eligible for registration under Article 7(1)(b) of Council Regulation (EC) No 40/94 of 20 December 1993 on the Community trade mark (OJ EC No 11 of 14.1.1994, p. 1) (hereinafter 'CTMR'). In his view the mark consisted of two descriptive words, 'BOLL' referring to the fruit of flax and cotton consisting of a capsule containing seeds, and 'GUARD', meaning to watch over, shield, or protect from danger and harm, which when combined did not confer on the mark a distinctive character. The mark used in relation to the goods in the application was clearly descriptive since it indicated that they had been developed to protect the boll from disease or infestation.

3. By fax of 28 January 1999, the applicant replied stating that the claimed mark was not directly descriptive and that the combination of the elements 'BOLL' and 'GARD' was sufficiently original and therefore distinctive as a trade mark.

4. By decision of 29 March 1999 (hereinafter 'the contested decision'), the examiner informed the applicant that the application was not eligible for registration under Article 7(1)(b) CTMR. The examiner justified his decision as follows:

> 'The mark is considered devoid of distinctive character as it merely describes significant characteristics of the goods namely that they protect the boll of certain plants from infestation or disease or that they are resistant to infestation or disease. This impression is immediately obvious notwithstanding the slight misspelling of the word "guard" or the fact that the mark is a combination of two words. An analysis of the component elements of a mark may be made when assessing a mark's overall impression. ...In this particular case the mark indicates the nature of the products directly and immediately and is therefore considered to be primarily descriptive and devoid of distinctive character. … A newly

> coined word or expression can still be devoid of any distinctive character if it is perceived as merely describing significant characteristics of the goods applied for. … *the fact that a trade mark is contrived, and as such is not found in a dictionary, does not preclude that mark from being descriptive*' [decision of 8 July 1998 in Case R 29/1998-3 – ENAMELIZE].

5. On 14 May 1999, the applicant filed a notice of appeal against the contested decision. The statement of the grounds of appeal was received on 23 July 1999.

6. Its arguments may be summarised as follows:

> 1. The combination of the words 'BOLL' and 'GARD', creates a word which does not exist in any dictionary in any language of the Community and is sufficiently novel and inventive as to give a limited degree of distinctiveness.
>
> 2. The mark is merely suggestive and is not directly descriptive, and no trader would wish to make use of this combination.
>
> 3. Registrations of the claimed mark in Spain and Greece for products in Classes 1 and 31 are an indication that absolute grounds for refusal are unlikely to exist and should be taken into account.

7. The appeal was submitted to the examiner for interlocutory revision pursuant to Article 60 CTMR on 26 July 1999. The Examination Division did not grant interlocutory revision and remitted the appeal to the Board on 3 August 1999.

8. Reference is made to the documents in the file including, in particular, the pleadings of the appellant, which have been considered by the Board and taken as a basis for its decision.

Reasons

9. The appeal complies with Articles 57, 58 and 59 CTMR and Rule 48(1) of Commission Regulation (EC) No 2868/95 of 13 December 1995 implementing the CTMR (OJ EC L 303 15.12.1995, p. 1). It is therefore admissible.

10. The issue to be decided is whether in the light of Article 7(1)(b) and (c) CTMR, the trade mark 'BOLLGARD' should be refused registration for the goods in the application. In that regard, an examination on absolute grounds must focus on the overall visual, aural and conceptual impression created by the mark, taking into account the presumed expectations of the average consumer, who is reasonably well informed and reasonably observant and circumspect.

11. Pursuant to Article 7(1)(b) CTMR, a trade mark which is devoid of any distinctive character, namely, one that is not capable of distinguishing the goods of one undertaking from those of another, cannot be registered. The essential function of a trade mark is to guarantee to the consumer the identity of the origin of the marked product, i.e. that all goods and services bearing it have originated from under the control of a single undertaking responsible for its quality (see judgment of the Court of Justice in Case C-39/97 *Canon Kabushiki Kaisha* v *Metro-Goldwyn-Mayer Inc.* [1998] ECR I-5507, paragraph 28). A trade mark must, therefore, be distinctive and be capable of serving as an indication of origin (see judgment of the Court of First Instance of 8 July 1999 in Case T-163/98 *The Procter and Gamble Company* v *OHIM*, paragraph 21).

12. Pursuant to Article 7 (1)(c) CTMR, 'trade marks which consist exclusively of indications which may serve, in trade, to designate the kind, quality, intended purpose… or other characteristics of the goods cannot be registered'. They must remain available for general use, since competitors have a legitimate interest in employing, without hindrance, in a descriptive manner

such indications relating to the very nature of the claimed goods.

13. An objection under Article 7 (1)(c) CTMR may, however, only be maintained where the descriptive content is immediately, clearly and unmistakably obvious from the application, particularly since experience shows that customers are unlikely to engage in a conceptual analysis of the trade marks they encounter in order to read descriptive meanings into them. It is more usual for consumers to accept trade marks, without much aforethought being given, as they appear on the market. If a term that could serve to describe the characteristics of goods is merely hinted at and is recognisable only on the basis of intellectual conclusions, it does not usually impede the registration (see decision of 26 February 1999 in Case R 71/1998-3 – PORTFOLIO, paragraph 10).

14. According to *Textile Terms and Definitions*, Tenth Edition, The Textile Institute, 1995, the word 'BOLL' refers to 'a seed-case and its contents on the cotton plant'. According to *A Dictionary of Natural Products* by George Macdonald Hocking, PH.D, Plexus 1997, the term 'BOLL' refers to a 'rounded capsule of cotton, flax'. The second element 'GARD' however has no dictionary meaning.

15. The Board considers that the claimed mark considered as a whole is unusual and sufficiently inventive since it is a combination of an arbitrary, imaginative and inventive element with another word, albeit descriptive. There is therefore no reason to hold that it is not capable of distinguishing the appellant's products from those of other undertakings, or that any undertaking should be reserved the right to use it in relation to competing products. Accordingly, it has a sufficient degree of minimal distinctiveness in order to be eligible for registration pursuant to Article 7(1)(b) CTMR.

16. Furthermore, the merger of the two elements in the claimed mark is not descriptive of any characteristic under Article 7(1)(c) CTMR. The term 'BOLLGARD' has no commercial meaning and would not obviously and immediately be taken as descriptive of any characteristic of the goods in the application. Nor would the registration of 'BOLLGARD' as a trade mark prevent the appellant's competitors from claiming that their goods are resistant to disease or infestation.

17. In addition, since the element 'GARD' is invented and is visually distinguishable from the word 'guard', the Board is not convinced that the relevant user would pronounce it in the same way as the word 'guard'. Nor would he automatically assume that the word 'gard' was a phonetic equivalent of the word 'guard'. Rather, he would make an association with the latter word only after aforethought. Accordingly, the Board considers that the relevant user confronted with the claimed mark used in connection with the products in the application will not have an immediate and precise idea that the products in the application will shield flax or cotton plants from disease or infestation. It is therefore not descriptive of the intended purpose of the products in the application under Article 7(1)(c) CTMR.

18. For the foregoing reasons, the contested decision must be set aside and the case is remitted to the examiner for further prosecution.

Order

For those reasons, it is decided that:

The decision of 29 March 1999 is set aside and the case is remitted to the examiner for further prosecution.

S. Sandri Th. Margellos A. Bender Registrar: L. McGarry

Annex One

Text of the Agreement on Trade-Related Aspects of Intellectual Property Rights 1994 (TRIPS)

Contents

Members,

Desiring to reduce distortions and impediments to international trade, and taking into account the need to promote effective and adequate protection of intellectual

property rights, and to ensure that measures and procedures to enforce intellectual property rights do not themselves become barriers to legitimate trade;

Recognizing, to this end, the need for new rules and disciplines concerning:
(a) the applicability of the basic principles of GATT 1994 and of relevant international intellectual property agreements or conventions;
(b) the provision of adequate standards and principles concerning the availability, scope and use of trade-related intellectual property rights;
(c) the provision of effective and appropriate means for the enforcement of trade-related intellectual property rights, taking into account differences in national legal systems;
(d) the provision of effective and expeditious procedures for the multilateral prevention and settlement of disputes between governments; and
(e) transitional arrangements aiming at the fullest participation in the results of the negotiations;

Recognizing the need for a multilateral framework of principles, rules and disciplines dealing with international trade in counterfeit goods;

Recognizing that intellectual property rights are private rights;

Recognizing the underlying public policy objectives of national systems for the protection of intellectual property, including developmental and technological objectives;

Recognizing also the special needs of the least-developed country Members in respect of maximum flexibility in the domestic implementation of laws and regulations in order to enable them to create a sound and viable technological base;

Emphasizing the importance of reducing tensions by reaching strengthened commitments to resolve disputes on trade-related intellectual property issues through multilateral procedures;

Desiring to establish a mutually supportive relationship between the WTO and the World Intellectual Property Organization (referred to in this Agreement as "WIPO") as well as other relevant international organizations;

Hereby agree as follows:

PART I: GENERAL PROVISIONS AND BASIC PRINCIPLES

Article 1 Nature and Scope of Obligations

1. Members shall give effect to the provisions of this Agreement. Members may, but shall not be obliged to, implement in their law more extensive protection than is

required by this Agreement, provided that such protection does not contravene the provisions of this Agreement. Members shall be free to determine the appropriate method of implementing the provisions of this Agreement within their own legal system and practice.

2. For the purposes of this Agreement, the term "intellectual property" refers to all categories of intellectual property that are the subject of Sections 1 through 7 of Part II.

3. Members shall accord the treatment provided for in this Agreement to the nationals of other Members. 1 In respect of the relevant intellectual property right, the nationals of other Members shall be understood as those natural or legal persons that would meet the criteria for eligibility for protection provided for in the Paris Convention (1967), the Berne Convention (1971), the Rome Convention and the Treaty on Intellectual Property in Respect of Integrated Circuits, were all Members of the WTO members of those conventions. 2 Any Member availing itself of the possibilities provided in paragraph 3 of Article 5 or paragraph 2 of Article 6 of the Rome Convention shall make a notification as foreseen in those provisions to the Council for Trade-Related Aspects of Intellectual Property Rights (the "Council for TRIPS").

Article 2 Intellectual Property Conventions

1. In respect of Parts II, III and IV of this Agreement, Members shall comply with Articles 1 through 12, and Article 19, of the Paris Convention (1967).

2. Nothing in Parts I to IV of this Agreement shall derogate from existing obligations that Members may have to each other under the Paris Convention, the Berne Convention, the Rome Convention and the Treaty on Intellectual Property in Respect of Integrated Circuits.

Article 3 National Treatment

1. Each Member shall accord to the nationals of other Members treatment no less favourable than that it accords to its own nationals with regard to the protection 3 of intellectual property, subject to the exceptions already provided in, respectively, the Paris Convention (1967), the Berne Convention (1971), the Rome Convention or the Treaty on Intellectual Property in Respect of Integrated Circuits. In respect of performers, producers of phonograms and broadcasting organizations, this obligation only applies in respect of the rights provided under this Agreement. Any Member availing itself of the possibilities provided in Article 6 of the Berne Convention (1971) or paragraph 1(b) of Article 16 of the Rome Convention shall make a notification as foreseen in those provisions to the Council for TRIPS.

2. Members may avail themselves of the exceptions permitted under paragraph 1 in relation to judicial and administrative procedures, including the designation of an address for service or the appointment of an agent within the jurisdiction of a Member, only where such exceptions are necessary to secure compliance with laws and regulations which are not inconsistent with the provisions of this Agreement and

where such practices are not applied in a manner which would constitute a disguised restriction on trade.

Article 4 Most-Favoured-Nation Treatment

With regard to the protection of intellectual property, any advantage, favour, privilege or immunity granted by a Member to the nationals of any other country shall be accorded immediately and unconditionally to the nationals of all other Members. Exempted from this obligation are any advantage, favour, privilege or immunity accorded by a Member:

(a) deriving from international agreements on judicial assistance or law enforcement of a general nature and not particularly confined to the protection of intellectual property;

(b) granted in accordance with the provisions of the Berne Convention (1971) or the Rome Convention authorizing that the treatment accorded be a function not of national treatment but of the treatment accorded in another country;

(c) in respect of the rights of performers, producers of phonograms and broadcasting organizations not provided under this Agreement;

(d) deriving from international agreements related to the protection of intellectual property which entered into force prior to the entry into force of the WTO Agreement, provided that such agreements are notified to the Council for TRIPS and do not constitute an arbitrary or unjustifiable discrimination against nationals of other Members.

Article 5 Multilateral Agreements on Acquisition or Maintenance of Protection

The obligations under Articles 3 and 4 do not apply to procedures provided in multilateral agreements concluded under the auspices of WIPO relating to the acquisition or maintenance of intellectual property rights.

Article 6 Exhaustion

For the purposes of dispute settlement under this Agreement, subject to the provisions of Articles 3 and 4 nothing in this Agreement shall be used to address the issue of the exhaustion of intellectual property rights.

Article 7 Objectives

The protection and enforcement of intellectual property rights should contribute to the promotion of technological innovation and to the transfer and dissemination of technology, to the mutual advantage of producers and users of technological knowledge and in a manner conducive to social and economic welfare, and to a balance of rights and obligations.

Article 8 Principles

1. Members may, in formulating or amending their laws and regulations, adopt measures necessary to protect public health and nutrition, and to promote the public interest in sectors of vital importance to their socio-economic and technological development, provided that such measures are consistent with the provisions of this Agreement.

2. Appropriate measures, provided that they are consistent with the provisions of this Agreement, may be needed to prevent the abuse of intellectual property rights by right holders or the resort to practices which unreasonably restrain trade or adversely affect the international transfer of technology.

PART II: STANDARDS CONCERNING THE AVAILABILITY, SCOPE AND USE OF INTELLECTUAL PROPERTY RIGHTS

SECTION 1: COPYRIGHT AND RELATED RIGHTS

Article 9 Relation to the Berne Convention

1. Members shall comply with Articles 1 through 21 of the Berne Convention (1971) and the Appendix thereto. However, Members shall not have rights or obligations under this Agreement in respect of the rights conferred under Article 6bis of that Convention or of the rights derived therefrom.

2. Copyright protection shall extend to expressions and not to ideas, procedures, methods of operation or mathematical concepts as such.

Article 10 Computer Programs and Compilations of Data

1. Computer programs, whether in source or object code, shall be protected as literary works under the Berne Convention (1971).

2. Compilations of data or other material, whether in machine readable or other form, which by reason of the selection or arrangement of their contents constitute intellectual creations shall be protected as such. Such protection, which shall not extend to the data or material itself, shall be without prejudice to any copyright subsisting in the data or material itself.

Article 11 Rental Rights

In respect of at least computer programs and cinematographic works, a Member shall provide authors and their successors in title the right to authorize or to prohibit the commercial rental to the public of originals or copies of their copyright works. A Member shall be excepted from this obligation in respect of cinematographic works unless such rental has led to widespread copying of such works which is materially impairing the exclusive right of reproduction conferred in that Member on authors and

their successors in title. In respect of computer programs, this obligation does not apply to rentals where the program itself is not the essential object of the rental.

Article 12 Term of Protection

Whenever the term of protection of a work, other than a photographic work or a work of applied art, is calculated on a basis other than the life of a natural person, such term shall be no less than 50 years from the end of the calendar year of authorized publication, or, failing such authorized publication within 50 years from the making of the work, 50 years from the end of the calendar year of making.

Article 13 Limitations and Exceptions

Members shall confine limitations or exceptions to exclusive rights to certain special cases which do not conflict with a normal exploitation of the work and do not unreasonably prejudice the legitimate interests of the right holder.

Article 14 Protection of Performers, Producers of Phonograms (Sound Recordings) and Broadcasting Organizations

1. In respect of a fixation of their performance on a phonogram, performers shall have the possibility of preventing the following acts when undertaken without their authorization: the fixation of their unfixed performance and the reproduction of such fixation. Performers shall also have the possibility of preventing the following acts when undertaken without their authorization: the broadcasting by wireless means and the communication to the public of their live performance.

2. Producers of phonograms shall enjoy the right to authorize or prohibit the direct or indirect reproduction of their phonograms.

3. Broadcasting organizations shall have the right to prohibit the following acts when undertaken without their authorization: the fixation, the reproduction of fixations, and the rebroadcasting by wireless means of broadcasts, as well as the communication to the public of television broadcasts of the same. Where Members do not grant such rights to broadcasting organizations, they shall provide owners of copyright in the subject matter of broadcasts with the possibility of preventing the above acts, subject to the provisions of the Berne Convention (1971).

4. The provisions of Article 11 in respect of computer programs shall apply mutatis mutandis to producers of phonograms and any other right holders in phonograms as determined in a Member's law. If on 15 April 1994 a Member has in force a system of equitable remuneration of right holders in respect of the rental of phonograms, it may maintain such system provided that the commercial rental of phonograms is not giving rise to the material impairment of the exclusive rights of reproduction of right holders.

5. The term of the protection available under this Agreement to performers and producers of phonograms shall last at least until the end of a period of 50 years computed from the end of the calendar year in which the fixation was made or the

performance took place. The term of protection granted pursuant to paragraph 3 shall last for at least 20 years from the end of the calendar year in which the broadcast took place.

6. Any Member may, in relation to the rights conferred under paragraphs 1, 2 and 3, provide for conditions, limitations, exceptions and reservations to the extent permitted by the Rome Convention. However, the provisions of Article 18 of the Berne Convention (1971) shall also apply, mutatis mutandis, to the rights of performers and producers of phonograms in phonograms.

SECTION 2: TRADEMARKS

Article 15 Protectable Subject Matter

1. Any sign, or any combination of signs, capable of distinguishing the goods or services of one undertaking from those of other undertakings, shall be capable of constituting a trademark. Such signs, in particular words including personal names, letters, numerals, figurative elements and combinations of colours as well as any combination of such signs, shall be eligible for registration as trademarks. Where signs are not inherently capable of distinguishing the relevant goods or services, Members may make registrability depend on distinctiveness acquired through use. Members may require, as a condition of registration, that signs be visually perceptible.

2. Paragraph 1 shall not be understood to prevent a Member from denying registration of a trademark on other grounds, provided that they do not derogate from the provisions of the Paris Convention (1967).

3. Members may make registrability depend on use. However, actual use of a trademark shall not be a condition for filing an application for registration. An application shall not be refused solely on the ground that intended use has not taken place before the expiry of a period of three years from the date of application.

4. The nature of the goods or services to which a trademark is to be applied shall in no case form an obstacle to registration of the trademark.

5. Members shall publish each trademark either before it is registered or promptly after it is registered and shall afford a reasonable opportunity for petitions to cancel the registration. In addition, Members may afford an opportunity for the registration of a trademark to be opposed.

Article 16 Rights Conferred

1. The owner of a registered trademark shall have the exclusive right to prevent all third parties not having the owner's consent from using in the course of trade identical or similar signs for goods or services which are identical or similar to those in respect of which the trademark is registered where such use would result in a likelihood of confusion. In case of the use of an identical sign for identical goods or services, a likelihood of confusion shall be presumed. The rights described above shall not

prejudice any existing prior rights, nor shall they affect the possibility of Members making rights available on the basis of use.

2. Article 6bis of the Paris Convention (1967) shall apply, mutatis mutandis, to services. In determining whether a trademark is well-known, Members shall take account of the knowledge of the trademark in the relevant sector of the public, including knowledge in the Member concerned which has been obtained as a result of the promotion of the trademark.

3. Article 6bis of the Paris Convention (1967) shall apply, mutatis mutandis, to goods or services which are not similar to those in respect of which a trademark is registered, provided that use of that trademark in relation to those goods or services would indicate a connection between those goods or services and the owner of the registered trademark and provided that the interests of the owner of the registered trademark are likely to be damaged by such use.

Article 17 Exceptions

Members may provide limited exceptions to the rights conferred by a trademark, such as fair use of descriptive terms, provided that such exceptions take account of the legitimate interests of the owner of the trademark and of third parties.

Article 18 Term of Protection

Initial registration, and each renewal of registration, of a trademark shall be for a term of no less than seven years. The registration of a trademark shall be renewable indefinitely.

Article 19 Requirement of Use

1. If use is required to maintain a registration, the registration may be cancelled only after an uninterrupted period of at least three years of non-use, unless valid reasons based on the existence of obstacles to such use are shown by the trademark owner. Circumstances arising independently of the will of the owner of the trademark which constitute an obstacle to the use of the trademark, such as import restrictions on or other government requirements for goods or services protected by the trademark, shall be recognized as valid reasons for non-use.

2. When subject to the control of its owner, use of a trademark by another person shall be recognized as use of the trademark for the purpose of maintaining the registration.

Article 20 Other Requirements

The use of a trademark in the course of trade shall not be unjustifiably encumbered by special requirements, such as use with another trademark, use in a special form or use in a manner detrimental to its capability to distinguish the goods or services of one undertaking from those of other undertakings. This will not preclude a requirement prescribing the use of the trademark identifying the undertaking producing the goods

or services along with, but without linking it to, the trademark distinguishing the specific goods or services in question of that undertaking.

Article 21 Licensing and Assignment

Members may determine conditions on the licensing and assignment of trademarks, it being understood that the compulsory licensing of trademarks shall not be permitted and that the owner of a registered trademark shall have the right to assign the trademark with or without the transfer of the business to which the trademark belongs.

SECTION 3: GEOGRAPHICAL INDICATIONS

Article 22 Protection of Geographical Indications

1. Geographical indications are, for the purposes of this Agreement, indications which identify a good as originating in the territory of a Member, or a region or locality in that territory, where a given quality, reputation or other characteristic of the good is essentially attributable to its geographical origin.

2. In respect of geographical indications, Members shall provide the legal means for interested parties to prevent:
(a) the use of any means in the designation or presentation of a good that indicates or suggests that the good in question originates in a geographical area other than the true place of origin in a manner which misleads the public as to the geographical origin of the good;
(b) any use which constitutes an act of unfair competition within the meaning of Article 10bis of the Paris Convention (1967).

3. A Member shall, ex officio if its legislation so permits or at the request of an interested party, refuse or invalidate the registration of a trademark which contains or consists of a geographical indication with respect to goods not originating in the territory indicated, if use of the indication in the trademark for such goods in that Member is of such a nature as to mislead the public as to the true place of origin.

4. The protection under paragraphs 1, 2 and 3 shall be applicable against a geographical indication which, although literally true as to the territory, region or locality in which the goods originate, falsely represents to the public that the goods originate in another territory.

Article 23 Additional Protection for Geographical Indications for Wines and Spirits

1. Each Member shall provide the legal means for interested parties to prevent use of a geographical indication identifying wines for wines not originating in the place indicated by the geographical indication in question or identifying spirits for spirits not originating in the place indicated by the geographical indication in question, even where the true origin of the goods is indicated or the geographical indication is used in translation or accompanied by expressions such as "kind", "type", "style", "imitation" or the like. 4

2. The registration of a trademark for wines which contains or consists of a geographical indication identifying wines or for spirits which contains or consists of a geographical indication identifying spirits shall be refused or invalidated, ex officio if a Member's legislation so permits or at the request of an interested party, with respect to such wines or spirits not having this origin.

3. In the case of homonymous geographical indications for wines, protection shall be accorded to each indication, subject to the provisions of paragraph 4 of Article 22. Each Member shall determine the practical conditions under which the homonymous indications in question will be differentiated from each other, taking into account the need to ensure equitable treatment of the producers concerned and that consumers are not misled.

4. In order to facilitate the protection of geographical indications for wines, negotiations shall be undertaken in the Council for TRIPS concerning the establishment of a multilateral system of notification and registration of geographical indications for wines eligible for protection in those Members participating in the system.

Article 24 International Negotiations; Exceptions

1. Members agree to enter into negotiations aimed at increasing the protection of individual geographical indications under Article 23. The provisions of paragraphs 4 through 8 below shall not be used by a Member to refuse to conduct negotiations or to conclude bilateral or multilateral agreements. In the context of such negotiations, Members shall be willing to consider the continued applicability of these provisions to individual geographical indications whose use was the subject of such negotiations.

2. The Council for TRIPS shall keep under review the application of the provisions of this Section; the first such review shall take place within two years of the entry into force of the WTO Agreement. Any matter affecting the compliance with the obligations under these provisions may be drawn to the attention of the Council, which, at the request of a Member, shall consult with any Member or Members in respect of such matter in respect of which it has not been possible to find a satisfactory solution through bilateral or plurilateral consultations between the Members concerned. The Council shall take such action as may be agreed to facilitate the operation and further the objectives of this Section.

3. In implementing this Section, a Member shall not diminish the protection of geographical indications that existed in that Member immediately prior to the date of entry into force of the WTO Agreement.

4. Nothing in this Section shall require a Member to prevent continued and similar use of a particular geographical indication of another Member identifying wines or spirits in connection with goods or services by any of its nationals or domiciliaries who have used that geographical indication in a continuous manner with regard to the same or related goods or services in the territory of that Member either (a) for at least 10 years preceding 15 April 1994 or (b) in good faith preceding that date.

5. Where a trademark has been applied for or registered in good faith, or where rights to a trademark have been acquired through use in good faith either:
(a) before the date of application of these provisions in that Member as defined in Part VI; or
(b) before the geographical indication is protected in its country of origin;
measures adopted to implement this Section shall not prejudice eligibility for or the validity of the registration of a trademark, or the right to use a trademark, on the basis that such a trademark is identical with, or similar to, a geographical indication.

6. Nothing in this Section shall require a Member to apply its provisions in respect of a geographical indication of any other Member with respect to goods or services for which the relevant indication is identical with the term customary in common language as the common name for such goods or services in the territory of that Member. Nothing in this Section shall require a Member to apply its provisions in respect of a geographical indication of any other Member with respect to products of the vine for which the relevant indication is identical with the customary name of a grape variety existing in the territory of that Member as of the date of entry into force of the WTO Agreement.

7. A Member may provide that any request made under this Section in connection with the use or registration of a trademark must be presented within five years after the adverse use of the protected indication has become generally known in that Member or after the date of registration of the trademark in that Member provided that the trademark has been published by that date, if such date is earlier than the date on which the adverse use became generally known in that Member, provided that the geographical indication is not used or registered in bad faith.

8. The provisions of this Section shall in no way prejudice the right of any person to use, in the course of trade, that person's name or the name of that person's predecessor in business, except where such name is used in such a manner as to mislead the public.

9. There shall be no obligation under this Agreement to protect geographical indications which are not or cease to be protected in their country of origin, or which have fallen into disuse in that country.

SECTION 4: INDUSTRIAL DESIGNS

Article 25 Requirements for Protection

1. Members shall provide for the protection of independently created industrial designs that are new or original. Members may provide that designs are not new or original if they do not significantly differ from known designs or combinations of known design features. Members may provide that such protection shall not extend to designs dictated essentially by technical or functional considerations.

2. Each Member shall ensure that requirements for securing protection for textile designs, in particular in regard to any cost, examination or publication, do not unreasonably impair the opportunity to seek and obtain such protection. Members

shall be free to meet this obligation through industrial design law or through copyright law.

Article 26 Protection

1. The owner of a protected industrial design shall have the right to prevent third parties not having the owner's consent from making, selling or importing articles bearing or embodying a design which is a copy, or substantially a copy, of the protected design, when such acts are undertaken for commercial purposes.

2. Members may provide limited exceptions to the protection of industrial designs, provided that such exceptions do not unreasonably conflict with the normal exploitation of protected industrial designs and do not unreasonably prejudice the legitimate interests of the owner of the protected design, taking account of the legitimate interests of third parties.

3. The duration of protection available shall amount to at least 10 years.

SECTION 5: PATENTS

Article 27 Patentable Subject Matter

1. Subject to the provisions of paragraphs 2 and 3, patents shall be available for any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application.[5] Subject to paragraph 4 of Article 65, paragraph 8 of Article 70 and paragraph 3 of this Article, patents shall be available and patent rights enjoyable without discrimination as to the place of invention, the field of technology and whether products are imported or locally produced.

2. Members may exclude from patentability inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect *ordre public* or morality, including to protect human, animal or plant life or health or to avoid serious prejudice to the environment, provided that such exclusion is not made merely because the exploitation is prohibited by their law.

3. Members may also exclude from patentability:
(a) diagnostic, therapeutic and surgical methods for the treatment of humans or animals;
(b) plants and animals other than micro-organisms, and essentially biological processes for the production of plants or animals other than non-biological and microbiological processes. However, Members shall provide for the protection of plant varieties either by patents or by an effective *sui generis* system or by any combination thereof. The provisions of this subparagraph shall be reviewed four years after the date of entry into force of the WTO Agreement.

Article 28 Rights Conferred

1. A patent shall confer on its owner the following exclusive rights:
(a) where the subject matter of a patent is a product, to prevent third parties not having the owner's consent from the acts of: making, using, offering for sale, selling, or importing[6] for these purposes that product;
(b) where the subject matter of a patent is a process, to prevent third parties not having the owner's consent from the act of using the process, and from the acts of: using, offering for sale, selling, or importing for these purposes at least the product obtained directly by that process.

2. Patent owners shall also have the right to assign, or transfer by succession, the patent and to conclude licensing contracts.

Article 29 Conditions on Patent Applicants

1. Members shall require that an applicant for a patent shall disclose the invention in a manner sufficiently clear and complete for the invention to be carried out by a person skilled in the art and may require the applicant to indicate the best mode for carrying out the invention known to the inventor at the filing date or, where priority is claimed, at the priority date of the application.

2. Members may require an applicant for a patent to provide information concerning the applicant's corresponding foreign applications and grants.

Article 30 Exceptions to Rights Conferred

Members may provide limited exceptions to the exclusive rights conferred by a patent, provided that such exceptions do not unreasonably conflict with a normal exploitation of the patent and do not unreasonably prejudice the legitimate interests of the patent owner, taking account of the legitimate interests of third parties.

Article 31 Other Use Without Authorization of the Right Holder

Where the law of a Member allows for other use[7] of the subject matter of a patent without the authorization of the right holder, including use by the government or third parties authorized by the government, the following provisions shall be respected:

(a) authorization of such use shall be considered on its individual merits;

(b) such use may only be permitted if, prior to such use, the proposed user has made efforts to obtain authorization from the right holder on reasonable commercial terms and conditions and that such efforts have not been successful within a reasonable period of time. This requirement may be waived by a Member in the case of a national emergency or other circumstances of extreme urgency or in cases of public non-commercial use. In situations of national emergency or other circumstances of extreme urgency, the right holder shall, nevertheless, be notified as soon as reasonably practicable. In the case of public non-commercial use, where the government or contractor, without making a patent search, knows or has

demonstrable grounds to know that a valid patent is or will be used by or for the government, the right holder shall be informed promptly;

(c) the scope and duration of such use shall be limited to the purpose for which it was authorized, and in the case of semi-conductor technology shall only be for public non-commercial use or to remedy a practice determined after judicial or administrative process to be anti-competitive;

(d) such use shall be non-exclusive;

(e) such use shall be non-assignable, except with that part of the enterprise or goodwill which enjoys such use;

(f) any such use shall be authorized predominantly for the supply of the domestic market of the Member authorizing such use;

(g) authorization for such use shall be liable, subject to adequate protection of the legitimate interests of the persons so authorized, to be terminated if and when the circumstances which led to it cease to exist and are unlikely to recur. The competent authority shall have the authority to review, upon motivated request, the continued existence of these circumstances;

(h) the right holder shall be paid adequate remuneration in the circumstances of each case, taking into account the economic value of the authorization;

(i) the legal validity of any decision relating to the authorization of such use shall be subject to judicial review or other independent review by a distinct higher authority in that Member;

(j) any decision relating to the remuneration provided in respect of such use shall be subject to judicial review or other independent review by a distinct higher authority in that Member;

(k) Members are not obliged to apply the conditions set forth in subparagraphs (b) and (f) where such use is permitted to remedy a practice determined after judicial or administrative process to be anti-competitive. The need to correct anti-competitive practices may be taken into account in determining the amount of remuneration in such cases. Competent authorities shall have the authority to refuse termination of authorization if and when the conditions which led to such authorization are likely to recur;

(l) where such use is authorized to permit the exploitation of a patent ("the second patent") which cannot be exploited without infringing another patent ("the first patent"), the following additional conditions shall apply:

> (i) the invention claimed in the second patent shall involve an important technical advance of considerable economic significance in relation to the invention claimed in the first patent;

(ii) the owner of the first patent shall be entitled to a cross-licence on reasonable terms to use the invention claimed in the second patent; and

(iii) the use authorized in respect of the first patent shall be non-assignable except with the assignment of the second patent.

Article 32 Revocation/Forfeiture

An opportunity for judicial review of any decision to revoke or forfeit a patent shall be available.

Article 33 Term of Protection

The term of protection available shall not end before the expiration of a period of twenty years counted from the filing date.8

Article 34 Process Patents: Burden of Proof

1. For the purposes of civil proceedings in respect of the infringement of the rights of the owner referred to in paragraph 1(b) of Article 28, if the subject matter of a patent is a process for obtaining a product, the judicial authorities shall have the authority to order the defendant to prove that the process to obtain an identical product is different from the patented process. Therefore, Members shall provide, in at least one of the following circumstances, that any identical product when produced without the consent of the patent owner shall, in the absence of proof to the contrary, be deemed to have been obtained by the patented process:

(a) if the product obtained by the patented process is new;

(b) if there is a substantial likelihood that the identical product was made by the process and the owner of the patent has been unable through reasonable efforts to determine the process actually used.

2. Any Member shall be free to provide that the burden of proof indicated in paragraph 1 shall be on the alleged infringer only if the condition referred to in subparagraph (a) is fulfilled or only if the condition referred to in subparagraph (b) is fulfilled.

3. In the adduction of proof to the contrary, the legitimate interests of defendants in protecting their manufacturing and business secrets shall be taken into account.

SECTION 6: LAYOUT-DESIGNS (TOPOGRAPHIES) OF INTEGRATED CIRCUITS

Article 35 Relation to the IPIC Treaty

Members agree to provide protection to the layout-designs (topographies) of integrated circuits (referred to in this Agreement as "layout-designs") in accordance with Articles 2 through 7 (other than paragraph 3 of Article 6), Article 12 and

paragraph 3 of Article 16 of the Treaty on Intellectual Property in Respect of Integrated Circuits and, in addition, to comply with the following provisions.

Article 36 Scope of the Protection

Subject to the provisions of paragraph 1 of Article 37, Members shall consider unlawful the following acts if performed without the authorization of the right holder:9 importing, selling, or otherwise distributing for commercial purposes a protected layout-design, an integrated circuit in which a protected layout-design is incorporated, or an article incorporating such an integrated circuit only in so far as it continues to contain an unlawfully reproduced layout-design.

Article 37 Acts Not Requiring the Authorization of the Right Holder

1. Notwithstanding Article 36, no Member shall consider unlawful the performance of any of the acts referred to in that Article in respect of an integrated circuit incorporating an unlawfully reproduced layout-design or any article incorporating such an integrated circuit where the person performing or ordering such acts did not know and had no reasonable ground to know, when acquiring the integrated circuit or article incorporating such an integrated circuit, that it incorporated an unlawfully reproduced layout-design. Members shall provide that, after the time that such person has received sufficient notice that the layout-design was unlawfully reproduced, that person may perform any of the acts with respect to the stock on hand or ordered before such time, but shall be liable to pay to the right holder a sum equivalent to a reasonable royalty such as would be payable under a freely negotiated licence in respect of such a layout-design.

2. The conditions set out in subparagraphs (a) through (k) of Article 31 shall apply mutatis mutandis in the event of any non-voluntary licensing of a layout-design or of its use by or for the government without the authorization of the right holder.

Article 38 Term of Protection

1. In Members requiring registration as a condition of protection, the term of protection of layout-designs shall not end before the expiration of a period of 10 years counted from the date of filing an application for registration or from the first commercial exploitation wherever in the world it occurs.

2. In Members not requiring registration as a condition for protection, layout-designs shall be protected for a term of no less than 10 years from the date of the first commercial exploitation wherever in the world it occurs.

3. Notwithstanding paragraphs 1 and 2, a Member may provide that protection shall lapse 15 years after the creation of the layout-design.

SECTION 7: PROTECTION OF UNDISCLOSED INFORMATION

Article 39

1. In the course of ensuring effective protection against unfair competition as provided in Article 10bis of the Paris Convention (1967), Members shall protect undisclosed information in accordance with paragraph 2 and data submitted to governments or governmental agencies in accordance with paragraph 3.

2. Natural and legal persons shall have the possibility of preventing information lawfully within their control from being disclosed to, acquired by, or used by others without their consent in a manner contrary to honest commercial practices[10] so long as such information:

(a) is secret in the sense that it is not, as a body or in the precise configuration and assembly of its components, generally known among or readily accessible to persons within the circles that normally deal with the kind of information in question;

(b) has commercial value because it is secret; and

(c) has been subject to reasonable steps under the circumstances, by the person lawfully in control of the information, to keep it secret.

3. Members, when requiring, as a condition of approving the marketing of pharmaceutical or of agricultural chemical products which utilize new chemical entities, the submission of undisclosed test or other data, the origination of which involves a considerable effort, shall protect such data against unfair commercial use. In addition, Members shall protect such data against disclosure, except where necessary to protect the public, or unless steps are taken to ensure that the data are protected against unfair commercial use.

SECTION 8: CONTROL OF ANTI-COMPETITIVE PRACTICES IN CONTRACTUAL LICENCES

Article 40

1. Members agree that some licensing practices or conditions pertaining to intellectual property rights which restrain competition may have adverse effects on trade and may impede the transfer and dissemination of technology.

2. Nothing in this Agreement shall prevent Members from specifying in their legislation licensing practices or conditions that may in particular cases constitute an abuse of intellectual property rights having an adverse effect on competition in the relevant market. As provided above, a Member may adopt, consistently with the other provisions of this Agreement, appropriate measures to prevent or control such practices, which may include for example exclusive grantback conditions, conditions preventing challenges to validity and coercive package licensing, in the light of the relevant laws and regulations of that Member.

3. Each Member shall enter, upon request, into consultations with any other Member which has cause to believe that an intellectual property right owner that is a national or domiciliary of the Member to which the request for consultations has been addressed is undertaking practices in violation of the requesting Member's laws and regulations on the subject matter of this Section, and which wishes to secure compliance with such legislation, without prejudice to any action under the law and to the full freedom of an ultimate decision of either Member. The Member addressed shall accord full and sympathetic consideration to, and shall afford adequate opportunity for, consultations with the requesting Member, and shall cooperate through supply of publicly available non-confidential information of relevance to the matter in question and of other information available to the Member, subject to domestic law and to the conclusion of mutually satisfactory agreements concerning the safeguarding of its confidentiality by the requesting Member.

4. A Member whose nationals or domiciliaries are subject to proceedings in another Member concerning alleged violation of that other Member's laws and regulations on the subject matter of this Section shall, upon request, be granted an opportunity for consultations by the other Member under the same conditions as those foreseen in paragraph 3.

PART III: ENFORCEMENT OF INTELLECTUAL PROPERTY RIGHTS

SECTION 1: GENERAL OBLIGATIONS

Article 41

1. Members shall ensure that enforcement procedures as specified in this Part are available under their law so as to permit effective action against any act of infringement of intellectual property rights covered by this Agreement, including expeditious remedies to prevent infringements and remedies which constitute a deterrent to further infringements. These procedures shall be applied in such a manner as to avoid the creation of barriers to legitimate trade and to provide for safeguards against their abuse.

2. Procedures concerning the enforcement of intellectual property rights shall be fair and equitable. They shall not be unnecessarily complicated or costly, or entail unreasonable time-limits or unwarranted delays.

3. Decisions on the merits of a case shall preferably be in writing and reasoned. They shall be made available at least to the parties to the proceeding without undue delay. Decisions on the merits of a case shall be based only on evidence in respect of which parties were offered the opportunity to be heard.

4. Parties to a proceeding shall have an opportunity for review by a judicial authority of final administrative decisions and, subject to jurisdictional provisions in a Member's law concerning the importance of a case, of at least the legal aspects of initial judicial decisions on the merits of a case. However, there shall be no obligation to provide an opportunity for review of acquittals in criminal cases.

5. It is understood that this Part does not create any obligation to put in place a judicial system for the enforcement of intellectual property rights distinct from that for the enforcement of law in general, nor does it affect the capacity of Members to enforce their law in general. Nothing in this Part creates any obligation with respect to the distribution of resources as between enforcement of intellectual property rights and the enforcement of law in general.

SECTION 2: CIVIL AND ADMINISTRATIVE PROCEDURES AND REMEDIES

Article 42 Fair and Equitable Procedures

Members shall make available to right holders[11] civil judicial procedures concerning the enforcement of any intellectual property right covered by this Agreement. Defendants shall have the right to written notice which is timely and contains sufficient detail, including the basis of the claims. Parties shall be allowed to be represented by independent legal counsel, and procedures shall not impose overly burdensome requirements concerning mandatory personal appearances. All parties to such procedures shall be duly entitled to substantiate their claims and to present all relevant evidence. The procedure shall provide a means to identify and protect confidential information, unless this would be contrary to existing constitutional requirements.

Article 43 Evidence

1. The judicial authorities shall have the authority, where a party has presented reasonably available evidence sufficient to support its claims and has specified evidence relevant to substantiation of its claims which lies in the control of the opposing party, to order that this evidence be produced by the opposing party, subject in appropriate cases to conditions which ensure the protection of confidential information.

2. In cases in which a party to a proceeding voluntarily and without good reason refuses access to, or otherwise does not provide necessary information within a reasonable period, or significantly impedes a procedure relating to an enforcement action, a Member may accord judicial authorities the authority to make preliminary and final determinations, affirmative or negative, on the basis of the information presented to them, including the complaint or the allegation presented by the party adversely affected by the denial of access to information, subject to providing the parties an opportunity to be heard on the allegations or evidence.

Article 44 Injunctions

1. The judicial authorities shall have the authority to order a party to desist from an infringement, inter alia to prevent the entry into the channels of commerce in their jurisdiction of imported goods that involve the infringement of an intellectual property right, immediately after customs clearance of such goods. Members are not obliged to accord such authority in respect of protected subject matter acquired or ordered by a person prior to knowing or having reasonable grounds to know that dealing in such subject matter would entail the infringement of an intellectual property right.

2. Notwithstanding the other provisions of this Part and provided that the provisions of Part II specifically addressing use by governments, or by third parties authorized by a government, without the authorization of the right holder are complied with, Members may limit the remedies available against such use to payment of remuneration in accordance with subparagraph (h) of Article 31. In other cases, the remedies under this Part shall apply or, where these remedies are inconsistent with a Member's law, declaratory judgments and adequate compensation shall be available.

Article 45 Damages

1. The judicial authorities shall have the authority to order the infringer to pay the right holder damages adequate to compensate for the injury the right holder has suffered because of an infringement of that person's intellectual property right by an infringer who knowingly, or with reasonable grounds to know, engaged in infringing activity.

2. The judicial authorities shall also have the authority to order the infringer to pay the right holder expenses, which may include appropriate attorney's fees. In appropriate cases, Members may authorize the judicial authorities to order recovery of profits and/or payment of pre-established damages even where the infringer did not knowingly, or with reasonable grounds to know, engage in infringing activity.

Article 46 Other Remedies

In order to create an effective deterrent to infringement, the judicial authorities shall have the authority to order that goods that they have found to be infringing be, without compensation of any sort, disposed of outside the channels of commerce in such a manner as to avoid any harm caused to the right holder, or, unless this would be contrary to existing constitutional requirements, destroyed. The judicial authorities shall also have the authority to order that materials and implements the predominant use of which has been in the creation of the infringing goods be, without compensation of any sort, disposed of outside the channels of commerce in such a manner as to minimize the risks of further infringements. In considering such requests, the need for proportionality between the seriousness of the infringement and the remedies ordered as well as the interests of third parties shall be taken into account. In regard to counterfeit trademark goods, the simple removal of the trademark unlawfully affixed shall not be sufficient, other than in exceptional cases, to permit release of the goods into the channels of commerce.

Article 47 Right of Information

Members may provide that the judicial authorities shall have the authority, unless this would be out of proportion to the seriousness of the infringement, to order the infringer to inform the right holder of the identity of third persons involved in the production and distribution of the infringing goods or services and of their channels of distribution.

Article 48 Indemnification of the Defendant

1. The judicial authorities shall have the authority to order a party at whose request measures were taken and who has abused enforcement procedures to provide to a party wrongfully enjoined or restrained adequate compensation for the injury suffered because of such abuse. The judicial authorities shall also have the authority to order the applicant to pay the defendant expenses, which may include appropriate attorney's fees.

2. In respect of the administration of any law pertaining to the protection or enforcement of intellectual property rights, Members shall only exempt both public authorities and officials from liability to appropriate remedial measures where actions are taken or intended in good faith in the course of the administration of that law.

Article 49 Administrative Procedures

To the extent that any civil remedy can be ordered as a result of administrative procedures on the merits of a case, such procedures shall conform to principles equivalent in substance to those set forth in this Section.

SECTION 3: PROVISIONAL MEASURES

Article 50

1. The judicial authorities shall have the authority to order prompt and effective provisional measures:

(a) to prevent an infringement of any intellectual property right from occurring, and in particular to prevent the entry into the channels of commerce in their jurisdiction of goods, including imported goods immediately after customs clearance;

(b) to preserve relevant evidence in regard to the alleged infringement.

2. The judicial authorities shall have the authority to adopt provisional measures *inaudita altera parte* where appropriate, in particular where any delay is likely to cause irreparable harm to the right holder, or where there is a demonstrable risk of evidence being destroyed.

3. The judicial authorities shall have the authority to require the applicant to provide any reasonably available evidence in order to satisfy themselves with a sufficient degree of certainty that the applicant is the right holder and that the applicant's right is being infringed or that such infringement is imminent, and to order the applicant to provide a security or equivalent assurance sufficient to protect the defendant and to prevent abuse.

4. Where provisional measures have been adopted *inaudita altera parte*, the parties affected shall be given notice, without delay after the execution of the measures at the latest. A review, including a right to be heard, shall take place upon request of the defendant with a view to deciding, within a reasonable period after the

notification of the measures, whether these measures shall be modified, revoked or confirmed.

5. The applicant may be required to supply other information necessary for the identification of the goods concerned by the authority that will execute the provisional measures.

6. Without prejudice to paragraph 4, provisional measures taken on the basis of paragraphs 1 and 2 shall, upon request by the defendant, be revoked or otherwise cease to have effect, if proceedings leading to a decision on the merits of the case are not initiated within a reasonable period, to be determined by the judicial authority ordering the measures where a Member's law so permits or, in the absence of such a determination, not to exceed 20 working days or 31 calendar days, whichever is the longer.

7. Where the provisional measures are revoked or where they lapse due to any act or omission by the applicant, or where it is subsequently found that there has been no infringement or threat of infringement of an intellectual property right, the judicial authorities shall have the authority to order the applicant, upon request of the defendant, to provide the defendant appropriate compensation for any injury caused by these measures.

8. To the extent that any provisional measure can be ordered as a result of administrative procedures, such procedures shall conform to principles equivalent in substance to those set forth in this Section.

SECTION 4: SPECIAL REQUIREMENTS RELATED TO BORDER MEASURES 12

Article 51 Suspension of Release by Customs Authorities

Members shall, in conformity with the provisions set out below, adopt procedures13 to enable a right holder, who has valid grounds for suspecting that the importation of counterfeit trademark or pirated copyright goods14 may take place, to lodge an application in writing with competent authorities, administrative or judicial, for the suspension by the customs authorities of the release into free circulation of such goods. Members may enable such an application to be made in respect of goods which involve other infringements of intellectual property rights, provided that the requirements of this Section are met. Members may also provide for corresponding procedures concerning the suspension by the customs authorities of the release of infringing goods destined for exportation from their territories.

Article 52 Application

Any right holder initiating the procedures under Article 51 shall be required to provide adequate evidence to satisfy the competent authorities that, under the laws of the country of importation, there is prima facie an infringement of the right holder's intellectual property right and to supply a sufficiently detailed description of the goods to make them readily recognizable by the customs authorities. The competent authorities shall inform the applicant within a reasonable period whether they have

accepted the application and, where determined by the competent authorities, the period for which the customs authorities will take action.

Article 53 Security or Equivalent Assurance

1. The competent authorities shall have the authority to require an applicant to provide a security or equivalent assurance sufficient to protect the defendant and the competent authorities and to prevent abuse. Such security or equivalent assurance shall not unreasonably deter recourse to these procedures.

2. Where pursuant to an application under this Section the release of goods involving industrial designs, patents, layout-designs or undisclosed information into free circulation has been suspended by customs authorities on the basis of a decision other than by a judicial or other independent authority, and the period provided for in Article 55 has expired without the granting of provisional relief by the duly empowered authority, and provided that all other conditions for importation have been complied with, the owner, importer, or consignee of such goods shall be entitled to their release on the posting of a security in an amount sufficient to protect the right holder for any infringement. Payment of such security shall not prejudice any other remedy available to the right holder, it being understood that the security shall be released if the right holder fails to pursue the right of action within a reasonable period of time.

Article 54 Notice of Suspension

The importer and the applicant shall be promptly notified of the suspension of the release of goods according to Article 51.

Article 55 Duration of Suspension

If, within a period not exceeding 10 working days after the applicant has been served notice of the suspension, the customs authorities have not been informed that proceedings leading to a decision on the merits of the case have been initiated by a party other than the defendant, or that the duly empowered authority has taken provisional measures prolonging the suspension of the release of the goods, the goods shall be released, provided that all other conditions for importation or exportation have been complied with; in appropriate cases, this time-limit may be extended by another 10 working days. If proceedings leading to a decision on the merits of the case have been initiated, a review, including a right to be heard, shall take place upon request of the defendant with a view to deciding, within a reasonable period, whether these measures shall be modified, revoked or confirmed. Notwithstanding the above, where the suspension of the release of goods is carried out or continued in accordance with a provisional judicial measure, the provisions of paragraph 6 of Article 50 shall apply.

Article 56 Indemnification of the Importer and of the Owner of the Goods

Relevant authorities shall have the authority to order the applicant to pay the importer, the consignee and the owner of the goods appropriate compensation for any

injury caused to them through the wrongful detention of goods or through the detention of goods released pursuant to Article 55.

Article 57 Right of Inspection and Information

Without prejudice to the protection of confidential information, Members shall provide the competent authorities the authority to give the right holder sufficient opportunity to have any goods detained by the customs authorities inspected in order to substantiate the right holder's claims. The competent authorities shall also have authority to give the importer an equivalent opportunity to have any such goods inspected. Where a positive determination has been made on the merits of a case, Members may provide the competent authorities the authority to inform the right holder of the names and addresses of the consignor, the importer and the consignee and of the quantity of the goods in question.

Article 58 Ex Officio Action

Where Members require competent authorities to act upon their own initiative and to suspend the release of goods in respect of which they have acquired prima facie evidence that an intellectual property right is being infringed:

(a) the competent authorities may at any time seek from the right holder any information that may assist them to exercise these powers;

(b) the importer and the right holder shall be promptly notified of the suspension. Where the importer has lodged an appeal against the suspension with the competent authorities, the suspension shall be subject to the conditions, mutatis mutandis, set out at Article 55;

(c) Members shall only exempt both public authorities and officials from liability to appropriate remedial measures where actions are taken or intended in good faith.

Article 59 Remedies

Without prejudice to other rights of action open to the right holder and subject to the right of the defendant to seek review by a judicial authority, competent authorities shall have the authority to order the destruction or disposal of infringing goods in accordance with the principles set out in Article 46. In regard to counterfeit trademark goods, the authorities shall not allow the re-exportation of the infringing goods in an unaltered state or subject them to a different customs procedure, other than in exceptional circumstances.

Article 60 De Minimis Imports

Members may exclude from the application of the above provisions small quantities of goods of a non-commercial nature contained in travellers' personal luggage or sent in small consignments.

SECTION 5: CRIMINAL PROCEDURES

Article 61

Members shall provide for criminal procedures and penalties to be applied at least in cases of wilful trademark counterfeiting or copyright piracy on a commercial scale. Remedies available shall include imprisonment and/or monetary fines sufficient to provide a deterrent, consistently with the level of penalties applied for crimes of a corresponding gravity. In appropriate cases, remedies available shall also include the seizure, forfeiture and destruction of the infringing goods and of any materials and implements the predominant use of which has been in the commission of the offence. Members may provide for criminal procedures and penalties to be applied in other cases of infringement of intellectual property rights, in particular where they are committed wilfully and on a commercial scale.

PART IV: ACQUISITION AND MAINTENANCE OF INTELLECTUAL PROPERTY RIGHTS AND RELATED INTER-PARTES PROCEDURES

Article 62

1. Members may require, as a condition of the acquisition or maintenance of the intellectual property rights provided for under Sections 2 through 6 of Part II, compliance with reasonable procedures and formalities. Such procedures and formalities shall be consistent with the provisions of this Agreement.

2. Where the acquisition of an intellectual property right is subject to the right being granted or registered, Members shall ensure that the procedures for grant or registration, subject to compliance with the substantive conditions for acquisition of the right, permit the granting or registration of the right within a reasonable period of time so as to avoid unwarranted curtailment of the period of protection.

3. Article 4 of the Paris Convention (1967) shall apply mutatis mutandis to service marks.

4. Procedures concerning the acquisition or maintenance of intellectual property rights and, where a Member's law provides for such procedures, administrative revocation and inter partes procedures such as opposition, revocation and cancellation, shall be governed by the general principles set out in paragraphs 2 and 3 of Article 41.

5. Final administrative decisions in any of the procedures referred to under paragraph 4 shall be subject to review by a judicial or quasi-judicial authority. However, there shall be no obligation to provide an opportunity for such review of decisions in cases of unsuccessful opposition or administrative revocation, provided that the grounds for such procedures can be the subject of invalidation procedures.

PART V: DISPUTE PREVENTION AND SETTLEMENT

Article 63 Transparency

1. Laws and regulations, and final judicial decisions and administrative rulings of general application, made effective by a Member pertaining to the subject matter of this Agreement (the availability, scope, acquisition, enforcement and prevention of the abuse of intellectual property rights) shall be published, or where such publication is not practicable made publicly available, in a national language, in such a manner as to enable governments and right holders to become acquainted with them. Agreements concerning the subject matter of this Agreement which are in force between the government or a governmental agency of a Member and the government or a governmental agency of another Member shall also be published.

2. Members shall notify the laws and regulations referred to in paragraph 1 to the Council for TRIPS in order to assist that Council in its review of the operation of this Agreement. The Council shall attempt to minimize the burden on Members in carrying out this obligation and may decide to waive the obligation to notify such laws and regulations directly to the Council if consultations with WIPO on the establishment of a common register containing these laws and regulations are successful. The Council shall also consider in this connection any action required regarding notifications pursuant to the obligations under this Agreement stemming from the provisions of Article 6ter of the Paris Convention (1967).

3. Each Member shall be prepared to supply, in response to a written request from another Member, information of the sort referred to in paragraph 1. A Member, having reason to believe that a specific judicial decision or administrative ruling or bilateral agreement in the area of intellectual property rights affects its rights under this Agreement, may also request in writing to be given access to or be informed in sufficient detail of such specific judicial decisions or administrative rulings or bilateral agreements.

4. Nothing in paragraphs 1, 2 and 3 shall require Members to disclose confidential information which would impede law enforcement or otherwise be contrary to the public interest or would prejudice the legitimate commercial interests of particular enterprises, public or private.

Article 64 Dispute Settlement

1. The provisions of Articles XXII and XXIII of GATT 1994 as elaborated and applied by the Dispute Settlement Understanding shall apply to consultations and the settlement of disputes under this Agreement except as otherwise specifically provided herein.

2. Subparagraphs 1(b) and 1(c) of Article XXIII of GATT 1994 shall not apply to the settlement of disputes under this Agreement for a period of five years from the date of entry into force of the WTO Agreement.

3. During the time period referred to in paragraph 2, the Council for TRIPS shall examine the scope and modalities for complaints of the type provided for under subparagraphs 1(b) and 1(c) of Article XXIII of GATT 1994 made pursuant to this

Agreement, and submit its recommendations to the Ministerial Conference for approval. Any decision of the Ministerial Conference to approve such recommendations or to extend the period in paragraph 2 shall be made only by consensus, and approved recommendations shall be effective for all Members without further formal acceptance process.

PART VI: TRANSITIONAL ARRANGEMENTS

Article 65 Transitional Arrangements

1. Subject to the provisions of paragraphs 2, 3 and 4, no Member shall be obliged to apply the provisions of this Agreement before the expiry of a general period of one year following the date of entry into force of the WTO Agreement.

2. A developing country Member is entitled to delay for a further period of four years the date of application, as defined in paragraph 1, of the provisions of this Agreement other than Articles 3, 4 and 5.

3. Any other Member which is in the process of transformation from a centrally-planned into a market, free-enterprise economy and which is undertaking structural reform of its intellectual property system and facing special problems in the preparation and implementation of intellectual property laws and regulations, may also benefit from a period of delay as foreseen in paragraph 2.

4. To the extent that a developing country Member is obliged by this Agreement to extend product patent protection to areas of technology not so protectable in its territory on the general date of application of this Agreement for that Member, as defined in paragraph 2, it may delay the application of the provisions on product patents of Section 5 of Part II to such areas of technology for an additional period of five years.

5. A Member availing itself of a transitional period under paragraphs 1, 2, 3 or 4 shall ensure that any changes in its laws, regulations and practice made during that period do not result in a lesser degree of consistency with the provisions of this Agreement.

Article 66 Least-Developed Country Members

1. In view of the special needs and requirements of least-developed country Members, their economic, financial and administrative constraints, and their need for flexibility to create a viable technological base, such Members shall not be required to apply the provisions of this Agreement, other than Articles 3, 4 and 5, for a period of 10 years from the date of application as defined under paragraph 1 of Article 65. The Council for TRIPS shall, upon duly motivated request by a least-developed country Member, accord extensions of this period.

2. Developed country Members shall provide incentives to enterprises and institutions in their territories for the purpose of promoting and encouraging technology transfer

to least-developed country Members in order to enable them to create a sound and viable technological base.

Article 67 Technical Cooperation

In order to facilitate the implementation of this Agreement, developed country Members shall provide, on request and on mutually agreed terms and conditions, technical and financial cooperation in favour of developing and least-developed country Members. Such cooperation shall include assistance in the preparation of laws and regulations on the protection and enforcement of intellectual property rights as well as on the prevention of their abuse, and shall include support regarding the establishment or reinforcement of domestic offices and agencies relevant to these matters, including the training of personnel.

PART VII: INSTITUTIONAL ARRANGEMENTS; FINAL PROVISIONS

Article 68 Council for Trade-Related Aspects of Intellectual Property Rights

The Council for TRIPS shall monitor the operation of this Agreement and, in particular, Members' compliance with their obligations hereunder, and shall afford Members the opportunity of consulting on matters relating to the trade-related aspects of intellectual property rights. It shall carry out such other responsibilities as assigned to it by the Members, and it shall, in particular, provide any assistance requested by them in the context of dispute settlement procedures. In carrying out its functions, the Council for TRIPS may consult with and seek information from any source it deems appropriate. In consultation with WIPO, the Council shall seek to establish, within one year of its first meeting, appropriate arrangements for cooperation with bodies of that Organization.

Article 69 International Cooperation

Members agree to cooperate with each other with a view to eliminating international trade in goods infringing intellectual property rights. For this purpose, they shall establish and notify contact points in their administrations and be ready to exchange information on trade in infringing goods. They shall, in particular, promote the exchange of information and cooperation between customs authorities with regard to trade in counterfeit trademark goods and pirated copyright goods.

Article 70 Protection of Existing Subject Matter

1. This Agreement does not give rise to obligations in respect of acts which occurred before the date of application of the Agreement for the Member in question.

2. Except as otherwise provided for in this Agreement, this Agreement gives rise to obligations in respect of all subject matter existing at the date of application of this Agreement for the Member in question, and which is protected in that Member on the said date, or which meets or comes subsequently to meet the criteria for protection

under the terms of this Agreement. In respect of this paragraph and paragraphs 3 and 4, copyright obligations with respect to existing works shall be solely determined under Article 18 of the Berne Convention (1971), and obligations with respect to the rights of producers of phonograms and performers in existing phonograms shall be determined solely under Article 18 of the Berne Convention (1971) as made applicable under paragraph 6 of Article 14 of this Agreement.

3. There shall be no obligation to restore protection to subject matter which on the date of application of this Agreement for the Member in question has fallen into the public domain.

4. In respect of any acts in respect of specific objects embodying protected subject matter which become infringing under the terms of legislation in conformity with this Agreement, and which were commenced, or in respect of which a significant investment was made, before the date of acceptance of the WTO Agreement by that Member, any Member may provide for a limitation of the remedies available to the right holder as to the continued performance of such acts after the date of application of this Agreement for that Member. In such cases the Member shall, however, at least provide for the payment of equitable remuneration.

5. A Member is not obliged to apply the provisions of Article 11 and of paragraph 4 of Article 14 with respect to originals or copies purchased prior to the date of application of this Agreement for that Member.

6. Members shall not be required to apply Article 31, or the requirement in paragraph 1 of Article 27 that patent rights shall be enjoyable without discrimination as to the field of technology, to use without the authorization of the right holder where authorization for such use was granted by the government before the date this Agreement became known.

7. In the case of intellectual property rights for which protection is conditional upon registration, applications for protection which are pending on the date of application of this Agreement for the Member in question shall be permitted to be amended to claim any enhanced protection provided under the provisions of this Agreement. Such amendments shall not include new matter.

8. Where a Member does not make available as of the date of entry into force of the WTO Agreement patent protection for pharmaceutical and agricultural chemical products commensurate with its obligations under Article 27, that Member shall:

(a) notwithstanding the provisions of Part VI, provide as from the date of entry into force of the WTO Agreement a means by which applications for patents for such inventions can be filed;

(b) apply to these applications, as of the date of application of this Agreement, the criteria for patentability as laid down in this Agreement as if those criteria were being applied on the date of filing in that Member or, where priority is available and claimed, the priority date of the application; and

(c) provide patent protection in accordance with this Agreement as from the grant of the patent and for the remainder of the patent term, counted from the filing date in accordance with Article 33 of this Agreement, for those of these applications that meet the criteria for protection referred to in subparagraph (b).

9. Where a product is the subject of a patent application in a Member in accordance with paragraph 8(a), exclusive marketing rights shall be granted, notwithstanding the provisions of Part VI, for a period of five years after obtaining marketing approval in that Member or until a product patent is granted or rejected in that Member, whichever period is shorter, provided that, subsequent to the entry into force of the WTO Agreement, a patent application has been filed and a patent granted for that product in another Member and marketing approval obtained in such other Member.

Article 71 Review and Amendment

1. The Council for TRIPS shall review the implementation of this Agreement after the expiration of the transitional period referred to in paragraph 2 of Article 65. The Council shall, having regard to the experience gained in its implementation, review it two years after that date, and at identical intervals thereafter. The Council may also undertake reviews in the light of any relevant new developments which might warrant modification or amendment of this Agreement.

2. Amendments merely serving the purpose of adjusting to higher levels of protection of intellectual property rights achieved, and in force, in other multilateral agreements and accepted under those agreements by all Members of the WTO may be referred to the Ministerial Conference for action in accordance with paragraph 6 of Article X of the WTO Agreement on the basis of a consensus proposal from the Council for TRIPS.

Article 72 Reservations

Reservations may not be entered in respect of any of the provisions of this Agreement without the consent of the other Members.

Article 73 Security Exceptions

Nothing in this Agreement shall be construed:

(a) to require a Member to furnish any information the disclosure of which it considers contrary to its essential security interests; or

(b) to prevent a Member from taking any action which it considers necessary for the protection of its essential security interests;

(i) relating to fissionable materials or the materials from which they are derived;

(ii) relating to the traffic in arms, ammunition and implements of war and to such traffic in other goods and materials as is carried on directly or indirectly for the purpose of supplying a military establishment;

(iii) taken in time of war or other emergency in international relations; or

(c) to prevent a Member from taking any action in pursuance of its obligations under the United Nations Charter for the maintenance of international peace and security.

Footnotes:

1. When "nationals" are referred to in this Agreement, they shall be deemed, in the case of a separate customs territory Member of the WTO, to mean persons, natural or legal, who are domiciled or who have a real and effective industrial or commercial establishment in that customs territory.

2. In this Agreement, "Paris Convention" refers to the Paris Convention for the Protection of Industrial Property; "Paris Convention (1967)" refers to the Stockholm Act of this Convention of 14 July 1967. "Berne Convention" refers to the Berne Convention for the Protection of Literary and Artistic Works; "Berne Convention (1971)" refers to the Paris Act of this Convention of 24 July 1971. "Rome Convention" refers to the International Convention for the Protection of Performers, Producers of Phonograms and Broadcasting Organizations, adopted at Rome on 26 October 1961. "Treaty on Intellectual Property in Respect of Integrated Circuits" (IPIC Treaty) refers to the Treaty on Intellectual Property in Respect of Integrated Circuits, adopted at Washington on 26 May 1989. "WTO Agreement" refers to the Agreement Establishing the WTO.

3. For the purposes of Articles 3 and 4, "protection" shall include matters affecting the availability, acquisition, scope, maintenance and enforcement of intellectual property rights as well as those matters affecting the use of intellectual property rights specifically addressed in this Agreement.

4. Notwithstanding the first sentence of Article 42, Members may, with respect to these obligations, instead provide for enforcement by administrative action.

5. For the purposes of this Article, the terms "inventive step" and "capable of industrial application" may be deemed by a Member to be synonymous with the terms "non-obvious" and "useful" respectively.

6. This right, like all other rights conferred under this Agreement in respect of the use, sale, importation or other distribution of goods, is subject to the provisions of Article 6.

7. "Other use" refers to use other than that allowed under Article 30.

8. It is understood that those Members which do not have a system of original grant may provide that the term of protection shall be computed from the filing date in the system of original grant.

9. The term "right holder" in this Section shall be understood as having the same meaning as the term "holder of the right" in the IPIC Treaty.

10. For the purpose of this provision, "a manner contrary to honest commercial practices" shall mean at least practices such as breach of contract, breach of confidence and inducement to breach, and includes the acquisition of undisclosed information by third parties who knew, or were grossly negligent in failing to know, that such practices were involved in the acquisition.

11. For the purpose of this Part, the term "right holder" includes federations and associations having legal standing to assert such rights.

12. Where a Member has dismantled substantially all controls over movement of goods across its border with another Member with which it forms part of a customs union, it shall not be required to apply the provisions of this Section at that border.

13. It is understood that there shall be no obligation to apply such procedures to imports of goods put on the market in another country by or with the consent of the right holder, or to goods in transit.

14. For the purposes of this Agreement:

(a) "counterfeit trademark goods" shall mean any goods, including packaging, bearing without authorization a trademark which is identical to the trademark validly registered in respect of such goods, or which cannot be distinguished in its essential aspects from such a trademark, and which thereby infringes the rights of the owner of the trademark in question under the law of the country of importation;

(b) "pirated copyright goods" shall mean any goods which are copies made without the consent of the right holder or person duly authorized by the right holder in the country of production and which are made directly or indirectly from an article where the making of that copy would have constituted an infringement of a copyright or a related right under the law of the country of importation.

Annex Two

Biotechnology and Intellectual Property Law in APEC economies

This annex provides information on particular IP practices relating to biotechnology in various APEC economies. Generally, it consists of publicly-available information, mostly on the web site of the intellectual property offices. Hence it varies widely in its scope and content. It is provided to give further insight into the range of approaches taken in the APEC region. The range is not complete, but reflects material made available to the editors at the time of compilation.

Following is information on:

- Australia
- Japan
- Republic of Korea
- New Zealand
- Singapore
- United States

Three other useful resources are:

- Intellectual Property Practices in the Field of Biotechnology
  OECD Document TD/TC/WP(98)15/FINAL
  Available on the OECD website (www.oecd.org)
- Trilateral Project: Comparative study on biotechnology patent practices
  Japanese, European and US patent offices
  Available on the JPO website (www.jpo.go.jp)
- Submissions to the WTO TRIPS Council on TRIPS Article 27.3b
  Documents in the series IP/C/W/125
  Available on the WTO website (docsonline.wto.org)

IP Australia
PATENTS - TRADE MARKS - DESIGNS

Patent Office

AUSTRALIAN PATENTS FOR: Microorganisms; Cell lines; Hybridomas; Related biological materials and their use; & Genetically manipulated organisms

Patentable subject matter

The range of patentable inventions involving microorganisms, cell lines, hybridomas and other related biological materials includes:

- bacteria and other procaryotes, fungi (inc. yeast), algae, protozoa, plasmids, viruses, prions;
- DNA, RNA, genes, viruses, vectors, chromosomes, prions, cell organelles and other nonliving material existing in, and reproducible from, microorganisms or like biological material;
- non-living material existing in and reproducible from a living cell, such as, monoclonal antibodies produced from hybridomas, DNA, RNA, genes, viruses, vectors, chromosomes, prions, cell organelles;
- purified nucleic acids.
- apparatus or processes for enzymology or microbiology;
- compositions of microorganisms or enzymes;
- propagating, preserving or maintaining microorganisms;
- mutation or genetic engineering;
- fermentation or enzyme using processes to synthesize a desired chemical compound or composition;
- measuring or testing processes involving enzymes or microorganisms;
- processes using enzymes or microorganisms to liberate, separate, purify or clean;
- the use of microorganisms to produce food or beverages.

Patent protection can also be obtained for inventions involving:

- genotypically or phenotypically modified living organisms. For example, genetically modified bacteria, plants and non-human organisms. Patenting of plant varieties is described in our information sheet *Australian Patents for Plants*;
- the building blocks of living matter, such as DNA and genes (including human DNA and genes) which have for the first time been identified and copied from their natural source and then manufactured synthetically as unique materials with a definite industrial use. DNA or genes in the human body are not patentable as such, however, a DNA or gene sequence which has been separated from the human body and manufactured synthetically for reintroduction into the human body for therapeutic purposes would be patentable. The treated human body is not patentable.
- products of such living matter eg. food supplements, drugs, and processes for synthesising the material or making the products.

The range of patentable inventions involving genetic manipulation found in Australian patent applications includes:

- synthetic genes or DNA sequences;
- mutant forms and fragments of gene sequences;
- the DNA coding sequence for a gene. This is claimed in either the isolated or recombinant state (otherwise it is claiming something which occurs in nature);
- the protein expressed by the gene;
- vectors (such as plasmids or bacteriophage vectors or viruses) containing the gene;
- probes for the gene;
- methods of transformation using the gene;
- anti-sense DNA (the opposite sequence to the gene, used for regulation of the gene);
- host cells carrying the gene;
- higher plants/animals carrying the gene;
- organisms for expression of the gene (making the protein from the DNA). There are many types of expression

systems:
  - bacterial, yeast, viral;
  - plant or animal cell cultures
  - higher plants or animals per se;
- DNA sequences can also include regulatory sequences such as promoters.
- general recombinant DNA methods such as PCR and novel expression systems.

"Human beings, and the biological processes for their generation" are not patentable, as they are specifically excluded under subsection 18(2) of the Patents Act 1990.

Patents

A patent is granted for an invention that is an innovative idea which provides a practical solution to a technological problem. In this context, a patent would only be granted for subject matter which meets all the following tests:

- involves the technical intervention of a technologist applying their inventive ingenuity to produce something distinguishable from the natural source material. (A patent cannot be granted for a mere discovery of biological material);
- is new in the sense of not previously being publicly available. That is, a patent cannot be granted for materials in their naturally occurring state or for materials which have previously been made publicly available;
- has been fully described in the sense that sufficient information is provided to allow the technologist to make the product or perform the process without having to resort to invention.
- has a demonstrated industrial use. The use to which the invention is to be put, for example, for the treatment of human diseases such as cancer or multiple sclerosis, must also be fully described. This means that there must be an actual use for an invention rather than speculation as to future uses.

The written description

The specification must include a full description of the microorganism, hybridoma, enzyme or transgenic material (including the organisms in which the transgenic products are expressed), and their use, as well as the best method of performing the invention known to the applicant.

Where the invention is a microorganism, enzyme or related material or a specific method to produce or use these materials, there should be sufficient details in the specification for a specialist in the field to identify and repeat the invention.

Applicants often have difficulty in satisfying the requirement to reproduce or repeat the invention and to fully describe biological materials such as microorganisms. To enable an applicant to meet this requirement applicants may choose to deposit the biological material under the provisions of the "Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure". This Treaty was devised to enable applicants to comply with this requirement by including references, in the patent specification, to Deposits under the Budapest Treaty.

Deposits of microorganisms must be made at an International Depositary Authority (IDA) in accordance with the rules of the Treaty on or before the filing date of the complete patent application. For more information on the Budapest Treaty see the information sheet *The Budapest Treaty and Australian Patents*.

Full description of the microorganism means an inclusion of the full morphological, biochemical and taxonomic characteristics of the organism known to the applicant. It also includes a full description of any scientific testing characteristics (e.g. isozyme analysis, DNA profiling, etc.), if available.

Where the invention is a plant or animal product or a specific method to produce such a product, there should be sufficient details in the specification for a specialist in the field to identify and repeat the invention (e.g. an isolated gene or a specific method to produce a transgenic product).

There must be sufficient clear information to enable the specialist to fill in any missing gaps in the description of the invention without conducting lots of experimentation or resorting to invention to discover the conditions necessary for the invention to work. Where the invention resides in a complete plant or animal (e.g. a mutated or transgenic plant variety) the entire organism must be described fully, with particular emphasis on the characteristics or combination of characteristics which are significantly different from known and related plants or animals.

Such a description would enable the plant or animal to be clearly identified and distinguished from known close relatives.

The description should also describe the method of selecting the invention from the other organisms produced in the transformation or mutation process.

Applicants should be wary of subjective descriptive characteristics (e.g. for plants - robust, tall, extensive, bright; or for micro-organisms - large, small, distinctive colonies, etc.). If there is no point of reference or objective standard, these terms will be meaningless.

Best method of performance

In order to satisfy full description requirements for an invention involving:

- new microorganisms,
- a process involving microorganisms, or
- products of microorganisms,

in addition to the broad description of the invention, all specific steps required to reproduce the microorganism, to carry out the processes or prepare the products must be disclosed in the specification. In other words, there may be a number of ways to achieve the desired result but the best way of obtaining the invented product or performing the invented process, must be described in detail.

For genetically manipulated organisms

In order to satisfy full description requirements, for example, in the case of an invention involving a transgenic plant or animal, in addition to the broad description of the invention all specific steps required to reproduce the genetic materials and the transgenic plants or animals must be disclosed in the specification. In other words, there may be a number of ways to achieve the desired result but the best way of obtaining the invented product or performing the invented process, must be described in detail.

Repeatability

A patent monopoly is granted in return for a full written description of an invention. Such a description is required to ensure that other people are able to make a product or repeat a process once the patent period is over. A specialist in the particular technology must be able to repeat the process or reproduce the product from the directions given in the written description.

The main difference between inventions involving living and non-living systems is that many processes involving living systems are not repeatable 100% of the time. In some cases the probability of repeating the invention, even using the best method known to the applicant, can be very low.

Each technological area has its own standard of repeatability and this must be taken into consideration when assessing repeatability of an invention. The issue when considering repeatability is not the numerical probability of achieving the specified result, but whether the result can be reproduced to a practical level acceptable to the person skilled in that particular technology.

In a case involving the “Scarlet Queen Elizabeth” rose, the method of production was a chance genetic mutation. It has been estimated that the chance of such a variety occurring is 1 in 100,000,000. If the unfortunate plant breeder who was trying to repeat the invention, had to rely on chance alone, he/she might have to examine up to 100,000,000 plants before he/she found the same variety again. The Patent Office would consider the process essentially unrepeatable and would not grant the patent.

However, in the last 40 odd years, we have learnt a lot more about genetic engineering. This means that although the chances of such a sport occurring remains the same, we are a lot better at:

- making such an event happen (mutagenesis); and
- finding the plant, once the sport has occurred from amongst all the other plants (selection).

On the other hand, some microbiological work done under automation and/or computer control over a period of time involves millions of trials, and such a number is clearly practical in the fields involved. In situations where the repeatability would be low (for example, production of plant varieties using standard breeding techniques), it is our practice to accept that there is a best method of performance, if there is a description of the process and a statement in the description such as:
"It is practical to repeat the invention using current state of the art techniques to carry out the number of trials necessary to achieve the desired result."

Repeatability is not likely to be an issue where the description of an invention, such as a novel organism, relies on a

deposit made under the Budapest Treaty.

The issue of repeatability is best considered through examples.

Mutagenesis

With our increased understanding of molecular inheritance of, for example, plant and animal characteristics, breeders now have an armoury of techniques to make mutational events occur more frequently - irradiation, drugs that alter the genetic coding for the characters, and sometimes manipulation of the genes for the characters themselves.

The use of these techniques means that repeatability is rarely an issue provided the inventor gives sufficient clear instructions for the specialist to follow and repeat the invention. The description would need to clearly identify the organisms used, the type and amount of mutagenic agent, and how the organism was treated and how the mutants were subsequently recovered.

Mutagenic chemicals

Under this umbrella, breeders have found that including the drug colchicine in the plant growth medium results in an increase in the number of plant chromosomes and often leads to an increase in flower size - a technique that rose breeders are now using. This change is readily described, is heritable and repeatable.

Other drugs have been used which specifically alter the genetic code of plants and such treatments have the effect of "hotting up" the rate of mutational events. One example of this from the patent literature is the treatment of wheat seed with several chemical mutagens, followed by screening the seedlings that survived the treatment for resistance to herbicide. Such wheat lines are of interest as farmers would then be able to spray their crops with the herbicide and specifically eradicate weed.

Genetic engineering

Another exciting approach has been through genetic engineering where genes are taken from one quite unrelated organism and put into a second. The use of genetic engineering requires that the plant breeder, for example, knows a great deal about the genes for the characters he/she wants to manipulate. Fortunately such knowledge is increasing rapidly. This approach permits not only the exquisitely accurate introduction of characteristics into plants but also the introduction of characteristics from unrelated species - impossible by the normal routes of sexual propagation. The description requires additional details about the genes used, such as for example, the sequence of the gene used to transform the organism. Repeatability is rarely an issue in genetic engineering inventions, provided the invention is fully described.

Other ingenious methods make use of unrelated characters, for example, a gene for a blue seed coat may be linked to a wanted characteristic so that if the plant receives the gene for one character, it also generally receives the other to the extent that the seed can be simply sorted by machine!

One important feature of this type of genetic manipulation is that instead of the breeder having to sift through the 100,000,000 plants, he/she can design his/her experiments so that the mutagenic events are no longer scattered throughout the plant genome but are concentrated only in the specific genes he/she wishes to alter.

Selection

The importance of selection is that instead of having to look at all 100,000,000 plants produced, the breeder can design breeding programs to eliminate over 90% of the unwanted plants and if he/she is really tricky, he/she can screen out almost all the unwanted plants. One example is the breeding of herbicide resistant wheat - the potentially disease resistant cultivars can be identified from their resistance to the herbicide when it is included in their culture medium. Susceptible plant cells die,
resistant ones survive - the breeder manipulates the odds spectacularly in his/her favour by simply killing off the few million or so plant cells that don't have the specific characteristic he/she wants.

The ability to select the required mutant organism generally obviates the issue of repeatability.

Some species are amenable to tissue culture techniques and this confers the added advantage that a very large number of "plants" can be examined on a culture plate the size of a saucer. A large array of crop plants are amenable to this technique, including both wheat and barley.

Patenting microorganisms and other biological materials

Patent claims to inventions relating to microorganisms may be directed to the microorganism itself, its products or processes, depending on where the novelty and inventive concept lie. The claims must be fairly based on a full description of the invention in the body of the specification.

The specific details required in a description of a new microorganism or related invention will vary depending on the nature of the particular invention claimed and must include information (data) clarifying the repeatability issue. The following is intended only as a guide to the applicant and is not an all-inclusive list of the sort of information needed.

New microorganisms, cell lines, hybridomas, etc.

If the invention is a microorganism per se, such as a bacterium or fungus, or a new cell line, etc, which may produce a desired product or have some desired effect (for example the ability of a microorganism to digest oil-spills), as much as is known of its features should be described.
This includes

- the taxonomic description
- morphological characteristics such as shape, size, stain ability, motility, etc
- colony characteristics, for example, colour, shape, size, swarming and any distinguishing features in appearance, such as shininess
- metabolic characteristics including substrate requirements, products or by-products, isozyme characteristics, etc
- genetic characterisation of any known genes relevant to the use or the characterisation of the organisation or the inventive concept. The characterisation may be at the level of gene sequence, function or restriction pattern.

Processes involving microorganisms, cell lines, hybridomas, etc.

When the invention lies in a process, such as fermentation, which makes use of a microorganism, the description of the invention should provide details including the particular organism used for the process as well as its required nutrient and culture conditions (temperature, aeration, etc.). If special incubation, mixing apparatus, or particular separation or isolation techniques are necessary to perform the invention, then they must be described in detail.

Products of microorganisms, cell lines, hybridomas, etc.

A microbial product, such as a novel antibiotic is best characterised by its structure. However, this is not always known so the product may be defined in terms of the organism from which it is produced and/or as many physical or chemical characteristics as are known and which are sufficient to distinguish it from other known compounds. Such information may be UV or IR absorption spectra, NMR spectrum, elemental analysis, molecular weight, melting point, solubility characteristics and HPLC analysis.

In all the above cases resort may be made to a deposit made under the Budapest Treaty in order to assist in fully describing the invention.

Patenting modified plants and animals

Patent claims which are directed to parts of inventive mature plants, animals or to plant seeds which grow into inventive mature organisms, must be limited by the characteristics of the mature organism. However, it may be possible to correlate certain characteristics of an organism (e.g. isoenzyme or DNA profiling analysis) with the inventive characteristics of the mature organism.

For example, where the invention claimed is a seed or a plant part of a material, such as, hybrid seed, transgenic plants, mutant plants and plant varieties, the full description must include information (data) clarifying the repeatability question and, at least, the following information:

Transgenic plants and animals

The characteristics of the gene introduced into the organisms must be described (preferably including the complete sequence of the gene) as well as the best method of transformation, regeneration and selection of the transformed materials, eg. protoplast, pollen or embryo. The parent strains or the source of the host material must also be fully described and readily available to the public.

Mutant plants and animals

The parent strains must be fully described and readily available to the public. The method of mutagenesis (e.g. chemical or UV radiation) and the method of selecting or obtaining the mutant organisms must be disclosed. Finally, there must be a full written description of the mutant produced. A deposit made under the Budapest Treaty may assist in this regard.

Where the invention is a component of a plant seed (e.g. an improved oleic/linoleic acid ratio) or is an improved characteristic of the seed (e.g. germination rates, viability, storability).

The method of manufacture of the seed must be disclosed in the specification and the source of the seed material must be fully described and readily available to the public. The description will not need to include the characteristics of the mature plant where these are not relevant. If breeding techniques are utilised then the description will require information similar to that required for plant varieties.

Any relevant characteristics of the seed must also be provided. The specification must also provide information (data) clarifying the repeatability question.

Similar requirements apply to transgenic or mutant animals and cell lines.

Seek professional advice

This sheet provides only basic information. Patenting biotechnology can sometimes involve complex legal issues and it may be in your best interests to obtain professional advice.

Example Patent Applications

(Application number and subject)
11198/92 Physiologically active Kanglemycin C, process for preparing the same and its use.
13186/92 Bioleaching of cobalt and copper containing pyritic concentrates.
13654/92 Biological reaction process.
17165/92 Method for detection of Dichelobactor Nodosus.
21122/92 Method for the rapid determination of the microorganism content of liquids and fluid solutions, and apparatus for implementing this method.
30088/92 Tumour associated monoclonal antibody 88BV59.
31277/93 Bacillus Thuringiensis isolates active against cockroaches and genes encoding cockroach-active toxins.
36856/93 Novel macrocyclic lactones and a productive strain thereof.
38200/93 Novel toxin producing fungal pathogen and uses.
35853/93 Biochemical purification of simvastatin.
36052/93 Mycobacterial species-specific reporter mycobacteriophages.
36709/93 Integrative gene-expression in food-grade microorganisms.
36925/93 Protein having nitrile hydratase activity and the gene encoding the same and a method for producing amides from nitriles via a transformant containing the gene.
36959/93 Fungal protease.
37166/93 Method for producing a microorganism which is natural enemy to a nematode.
62066/94 New Bacillus Thuringensis strains and their insecticidal proteins.
66810/94 Method for addressing proteins in yeast.
72119/94 Glycolate oxidase production.
11019/95 Aspergillus expression system.
21913/95 Novel mutated virus and novel methods of making vaccines.
41569/96 Insecticidal compositions containing heterorhabditis nematodes.
47637/96 Human retinoid X receptor - gamma (hRXR - gamma)
57576/90 transgenic animal producing modified human granulocyte macrophage-colony stimulating factor.
81063/91 transgenic animals generated using embryos passaged in culture medium containing Lif.
13703/92 gene construct for transgenic fish
17429/92 non-human animal carrying non-infectious HIV genome.
19530/92 genetic sequences encoding flavonoid pathway enzymes
26766/92 Transgenic plants.
34025/93 Virus resistant animals using pseudorabies virus polynucleotides.

36303/93 Transgenic Wheat
51356/93 Transgenic animal models for neurodegenrative disease.
62558/94 Animals with disrupted colony stimulating factors production.
76194/94 Plants with a DNA construct to modify expression of senescence gene.
80226/94 Novel cruciferous plant having a high carotene content.
10758/95 Double knockout transgenic mammal as a model for sepsis.
19770/95 Production of fibrinogen in tansgenic animals.
20022/95 Recombinant saccharomyces for decreased hydrogen sulfide formation in beer production.
46884/96 Genetically modified plant with modulated flower meristem.
47028/96 Plant transformed with bacterio-opsin gene for pathogen resistance.
47851/96 Transgenic animals with defective thyroid hormone receptor gene.
52245/96 Plants with a disrupted stamen cell function or development.
17257/97 Parapoxviruses containing foreign DNA.
17502/97 Humanised green flourescent protein genes.
17559/97 Rasberry promters for expression of transgenes in plants.
63837/98 Mammalian melanocyte stimulating hormone receptors.
78438/98 Culturing algae such as Spirulina.

You can read these applications at any IP AUSTRALIA State Office. Or you can order a copy from our Examination Support and Sales Unit in Canberra, phone (02) 6283 2355 for more information.

JAPAN
PROVISIONAL TRANSLATION[1]

Implementing Guidelines for Inventions in Specific Fields

Chapter 2 Biological Inventions

In this chapter, matters requiring special judgment and handling in examining patent applications relating to biological inventions are mainly explained.

Here, the term "organisms" means microorganisms, animals as well as plants, including reproducible animal or plant cells.

In this chapter, "Implementing Guidelines" means "Section 1. Implementing Guidelines for 1994-Revised Section 36 of the Patent Law" in "Practices in Examination and Appeals under 1994-Revised Patent Law (May 1995, the Japanese Patent Office)."

1. GENETIC ENGINEERING

This section deals with inventions relating to genetic engineering in biological inventions. The term "genetic engineering" here means the technology which manipulates genes artificially by gene recombination, cell fusion, etc.

Inventions relating to genetic engineering include those of a gene, a vector, a recombinant vector, a transformant, a fused cell, a protein which are obtained by transformation (hereinafter, referred to as "a recombinant protein"), a monoclonal antibody, etc.

Inventions relating to microorganisms, plants and animals, and which are obtained using genetic engineering are treated here in this section, in principle.

1.1 Description Requirements for the Specification

1.1.1 Scope of Claim (See Implementing Guidelines, Chapter 1-2.2.2.)

According to Section 36(6)(ii) of the Patent Law, the invention for which a patent is sought shall be clear, therefore, scope of claim shall be described that an invention shall be clearly identified on the basis of statements of each claim.

In a claim, a gene, a vector, a recombinant vector, a transformant, a fused cell, a recombinant protein and a monoclonal antibody should be described as indicated below.

(1) Genes

1) A gene may be described by specifying its base sequence.

2) A structural gene may be described by specifying an amino acid sequence of the protein encoded by the said gene.

Example: A gene encoding a protein consisting of an amino acid sequence represented by Met-Asp-??????-Lys-Glu.

3) A gene may be described by a combination of the terms "substitution, deletion or addition" or "hybridize" and functions of the gene, and if necessary, origin or source of the gene in a generic form as follows (provided that the claimed invention is clear and the enablement requirement is met (See 1.1.2.1 below)).

Example 1:

[1] When any ambiguity of interpretation is found in this translation the Japanese text shall prevail

A gene encoding a protein of (a) or (b) as follows:
(a) a protein whose amino acid sequence is represented by Met-Tyr-??????-Cys-Leu
(b) a protein derived from the protein of (a) by substitution, deletion or addition of one or several amino acids in the amino acid sequence defined in (a) and having the activity of enzyme A.

Note: The protein (a) has the activity of enzyme A.
The gene encoding the protein (b) is described in the detailed description of the invention in such a manner that a person skilled in the art can make the said gene without large amount of trials and errors or complicated experimentations beyond the reasonable extent that can be expected from a person skilled in the art who is supposed to have ordinary skill.

Example 2:
A gene selected from the group consisting of:
(a) a DNA whose nucleotide sequence is represented by ATGTATCGG???TGCCT
(b) a DNA which hybridizes under stringent conditions to the DNA defined in (a) and encodes the human protein having the activity of enzyme B.

Note: A protein encoded by the DNA (a) has the activity of enzyme B.
"Stringent conditions" are described in the detailed description of the invention.

4) A gene may be described by specifying functions, physiochemical properties, origin or source of the said gene, a process for producing the said gene, etc. (provided that the claimed invention is clear and the enablement requirement is met (See 1.1.2.1 below)).

(2) Vector

A vector should be described by specifying a base sequence of its DNA, a cleavage map of DNA, molecular weight, number of base pairs, source of the vector, process for producing the vector, function or characteristics of the vector, etc.

Note: A cleavage map is a map which shows the relative location and distance of the cleavage sites by various restriction enzymes.

(3) Recombinant vector

A recombinant vector may be described by specifying at least one of the gene and the vector.

Example: A recombinant vector containing a DNA whose base sequence is represented by ACAGCA??????AGTCAC.

(4) Transformant

A transformant may be described by specifying at least one of 1) its host and 2) the gene which is introduced (or the recombinant vector) (provided the that the daimed invention is clear and enablement requirement is met (See 1.1.2.1 below)).

Example 1:
A transformant comprising a recombinant vector containing a gene encoding a protein whose amino acid sequence is represented by Met-Asp-??????Lys-Glu.

Example 2:
A plant wherein a toxin gene having a base sequence of ATGACT?????? is inserted and the said gene is expressed.

Example 3:
A transgenic non-human mammal, having a recombinant DNA obtained by linking a structural gene encoding any protein to the regulatory region of a gene involved in the production of milk protein, and secreting the said protein into milk.

(5) Fused cell

A fused cell may be described by specifying parent cells, function and characteristics of the fused cell, or a process for producing the fused cell, etc.

(6) Recombinant protein

1) A recombinant protein may be described by specifying an amino acid sequence or a base sequence of structural gene encoding the said amino acid sequence.

Example:
A recombinant protein consisting of an amino acid sequence represented by Met-Tyr-??????-Cys-Leu.

2) A recombinant protein may be described by a combination of the terms "substitution, deletion or addition" and functions of the recombinant protein, and if necessary, origin or source of the recombinant protein in a generic form as follows (provided that the claimed invention is clear and the enablement requirement is met (See 1.1.2.1 below)).

Example:
A recombinant protein of (a) or (b) as follows:
(a) a protein whose amino acid sequence is represented by Met-Tyr-…….-Cys-Leu
(b) a protein derived from the protein of (a) by substitution, deletion or addition of one or several amino acids in the amino acid sequence in(a) and having the activity of enzyme A.

Note: A protein (a) has the activity of enzyme A.
The protein (b) is described in the detailed description of the invention in such a manner that a person skilled in the art can make the said protein without a large amount of trials and errors or complicated experimentations beyond the reasonable extent that can be expected from a person skilled in the art who is supposed to have ordinary skill.

3) A recombinant protein may be described by specifying functions, physiochemical, origin or source of the said recombinant protein, a process for producing the said recombinant protein, etc. (provided that the claimed invention is clear and the enablement requirement is met (See 1.1.2.1 below)).

(7) Monoclonal antibody

A claim directed a monoclonal antibody may be defined by specifying any of antigen recognized by it, hybridoma which produces it, or cross-reactivity, etc.

Example 1:
A monoclonal antibody to antigen A.
[Note] Antigen A is necessary to be defined by specifying as a substance.

Example 2:
A monoclonal antibody to antigen A, produced by a hybridoma having ATCC Deposit No. HB-xxxx.
[Note] Antigen A is necessary to be defined by specifying as a substance.

Example 3:
A monoclonal antibody which binds not to antigen B but to antigen A.
[Note] Antigen A and antigen B are necessary to be defined by specifying as substances.

1.1.2 The Detailed Description of the Invention (See Implementing Guidelines, Chapter 1-3.)

The detailed description of the invention shall be stated in such a manner sufficiently clear and complete for the invention to be carried out by a person having ordinary skill in the art to which the invention pertains (the enablement requirement), and shall be stated that the problem to be solved by the invention and its solution, or other matters necessary for a person having ordinary skill in the art to understand the technical significance of the invention (the Ministerial Ordinance Requirement).
The detailed description of the invention which does not meet the above requirements violates Section 36(4) of the Patent Law.

1.1.2.1 Enablement Requirement (See Implementing Guidelines, Chapter 1-3.2.)

Section 36(4) of the Patent Law states that "the detailed description of the invention shall be stated .... in such a manner sufficiently clear and complete for the invention to be carried out by a person having ordinary skill in the art to which the invention pertains."

This means that "the detailed description of the invention shall be described in such a manner that a person who has ability to use ordinary technical means for research and development (including comprehension of document, experimentation, analysis and manufacture) and to exercise ordinary creativity in the art to which the invention pertains can carry out the claimed invention on the basis of matters described in the specification (excluding claims) and drawings taking into consideration the common general knowledge as of the filing."

Therefore, if "a person skilled in the art" who is supposed to have ordinary skill cannot understand how to carry out the invention on the basis of teachings in the specification (excluding claims) and drawings taking into consideration the common general knowledge as of the filing, then, such a description of the invention should be deemed insufficient for enabling such a person to carry out the invention. For example, if a large amount of trials and errors or complicated experimentations are needed to find a way of carrying out the invention beyond the reasonable extent that can be expected from a person skilled in the art who is supposed to have ordinary skill, the detailed description of the invention is not described in such a manner that enables a person skilled in the art to carry out the invention.

1.1.2.1.1 An Invention of a Product (See Implementing Guidelines, Chapter 1-3.2.1(2).)

For an invention of a product, the definition of carrying out the invention is to make and use the product. That a product can be used is interpreted as meaning that a product can be used in an industrially applicable way. Also, the said invention of a product should be explained clearly in the detailed description of the invention.

Therefore, an invention of a gene, a vector, a recombinant vector, a transformant, a fused cell, a recombinant protein, a monoclonal antibody, etc. should be described as follows.

(1) "An invention of a product" being explained clearly

If an invention of a product can be identified by a person skilled in the art based on the statements of a claim and can be understood from the statements and implications in the detailed description of the invention, then, the invention will be deemed as being explained clearly.

(2) "Can be made"

For an invention of a gene, a vector, a recombinant vector, a transformant, a fused cell, a recombinant protein or a monoclonal antibody, the way of making the product shall be described in the detailed description of the invention except where the product could be made by a person skilled in the art without such description when taking into account the overall descriptions of the specification (excluding claims), drawings and common general knowledge as of the filing.

1) Gene, vector or recombinant vector

A process for producing a gene, a vector or a recombinant vector should be described by respective origin or source, means for obtaining a vector to be used, an enzyme to be used, treatment conditions, steps for collecting and purifying it, or means for identification, etc.

If genes are claimed in a generic form (See 1.1.1(1)3)) and a large amount of trials and errors or complicated experimentations are needed to produce those genes beyond the reasonable extent that can be expected from a person skilled in the art, the detailed description of the invention is not described in such a manner that enables a person skilled in the art to make the product.

For example, in case that a claimed invention includes the gene actually obtained and many of genes whose identity is extremely low to the said gene obtained and is specified by their function and that as a result, many of genes which do not have the same function as the said gene obtained are included in the genes whose identity is extremely low, a large amount of trials and errors or complicated experimentations are generally needed to select the genes with the same function as the said gene obtained among the genes whose identity is extremely low beyond the reasonable extent that can be expected from a person skilled in the art, and therefore, the detailed description of the invention is not described in such a manner that enables a person skilled in the art to make the product.

Example: A gene selected from the group consisting of:
(a) a DNA whose nucleotide sequence is represented by ATGTATCGG…TGCCT

(b) a DNA whose nucleotide sequence has more than X% identity to that of (a) and which encodes the protein having the activity of enzyme B.

Note: A protein encoded by the DNA (a) has the activity of enzyme B.
X% represents extremely low identity.

Explanation: Genes whose identity is extremely low to the gene actually obtained are included in the (b), although (b) is specified by its function. In case that " A DNA whose nucleotide sequence has more than X % identity to that of (a)" includes many of genes which do not have the activity of enzyme B, a large amount of trials and errors or complicated experimentations are generally needed to select the genes with the activity of enzyme B beyond the reasonable extent that can be expected from a person skilled in the art. Therefore, the detailed description of the invention is not described in such a manner that enables a person skilled in the art to make the product.

2) Transformant

A process for producing a transformant should be described by a gene or a recombinant vector introduced, a host (a microorganism, a plant or an animal), a method of introducing gene or the recombinant vector into the host, a method of selectively collecting the transformant, or means for identification, etc.

If the transformant is the one described by a generic taxonomical unit (e.g., a transformed plant, a transformed non-human vertebrate, a transformant (including microorganisms, plants and animals)), and if a large amount of trials and errors or complicated experimentations are needed to produce those transformants beyond the reasonable extent that can be expected from a person skilled in the art, the detailed description of the invention is not described in such a manner that enables a person skilled in the art to make the product.

3) Fused cell

A process for producing a fused cell should be described by stating pretreatment of the parent cells, fusion condition, a method of selectively collecting the fused cell, or means for identification, etc.

4) Recombinant protein

A process for producing a recombinant protein should be described by stating means for obtaining a gene encoding the recombinant protein means for obtaining, an expression vector used, means for obtaining a host, a method for introducing the gene into the host, steps for collecting and purifying the recombinant protein from the transformant into which the gene has been introduced, or means for identification of the obtained recombinant protein, etc.

(See "1) Gene, vector or recombinant vector" for the treatment of enablement requirement in case that recombinant proteins are claimed in a generic form.)

5) Monoclonal antibody

A process for producing a monoclonal antibody should be described by stating means for obtaining or producing immunogen, a method for immunization, a process for selectively obtaining antibody producing cells, or means for identification of the monoclonal antibody, etc.

6) Deposit of microorganisms, etc. (For the detail of deposit and furnishing of microorganisms etc., see 2.1.3.1.1 (2) 1) Deposit and Furnishing of Microorganisms.)

(a) For an invention of a gene, a vector, a recombinant vector, a transformant, a fused cell, a recombinant protein, a monoclonal antibody, etc. produced by the use of a microorganism, etc. ("a microorganism, etc." here includes a microorganism, a plant and an animal), a process for producing the said product should be described in the specification as filed so that a person skilled in the art can make it. Further, the microorganism used in the process should be deposited and its accession number should be described in the specification as filed unless the microorganisms readily available to a person skilled in the art (See 2.1.3.1.1(2) 1)(ii)).

(b) For an invention of a gene, a vector, a recombinant vector, a transformant, a fused cell, a recombinant protein, a monoclonal antibody, etc., when it is not possible to describe a process for producing the said product in the specification in such a manner that a person skilled in the art can make it, the obtained transformant (including a transformant which produces a recombinant protein) or the fused cell (including a hybridoma which produces a monoclonal antibody) into which the gene, the vector, the recombinant vector has been introduced, should be deposited and its accession number should be described in the specification as filed.

(c) Generally, the obtainment of a hybridoma producing a monoclonal antibody which satisfies limitative conditions, (e.g., a monoclonal antibody whose affinity to the antigen A is specified by the limitative coupling constant,) is not reproducible. Therefore, in case that the claimed invention is related to a monoclonal antibody

which satisfies limitative conditions or a hybridoma producing the said monoclonal antibody, the said hybridoma should be deposited and its accession number should be described in the specification as filed, except where the hybridoma can be created by a person skilled in the art on the basis of the description in the specification.

(3) "Can be used"

For an invention of a gene, a vector, a recombinant vector, a transformant, a fused cell, a recombinant protein, a monoclonal antibody, etc., in order to show the industrial applicability of the product, the way of industrial application of it shall be described in the detailed description of the invention except where it could be understood by a person skilled in the art without such description when taking into account the overall descriptions of the specification (excluding claims), drawings and common general knowledge as of the filing.
For instance, in order to show the industrial applicability of the invention of a gene, it should be described in the detailed description of the invention that the gene has the specific function (in case of a structural gene, the protein encoded by the said gene has the specific function).

In case that genes are claimed in a generic form and the function is not specified in the claim (genes specified only by "substituted, deleted or added," "hybridized" or "having more than X% identity," etc.), the genes claimed in a generic form contain the ones which do not have the said function and the part of the said genes cannot be used, and therefore, the detailed description of the invention is not described in such a manner that enables a person skilled in the art to use the product.

1.1.2.1.2 An Invention of a Process (See Implementing Guidelines, Chapter 1-3.2.1(3).)

For an invention of a process, the definition of carrying out the invention is to use the process and that a process can be used is interpreted as meaning that a process can be used in an industrially applicable way. Further, the said invention of a process should be explained clearly in the detailed description of the invention. In order to describe the invention of the process in such a manner that the process can be used in an industrially applicable way, the enablement requirement in "1.1.2.1.1 An Invention of a Product" should be referred to, if necessary. For instance, "1.1.2.1.1(2) 6) Deposit of microorganisms, etc." should be referred to if deposit of microorganisms, etc. is necessary.

1.1.2.1.3 An Invention of a Process for Manufacturing a Product[2]

Where an invention of a process is directed to "a process for manufacturing a product," the definition of "the process can be used" means that the product can be manufactured by the process and either the process or the product shall be industrially applicable to meet industrial application. Further, the said invention of a process for manufacturing a product should be explained clearly.

Therefore, for an invention of a process for producing a gene, a vector, a recombinant vector, a transformant, a fused cell, a recombinant protein, a monoclonal antibody, etc., the said process should be explained clearly and the description shall be stated so as to enable a person skilled in the art to produce the product by using the said process. In order to be stated so as to enable a person skilled in the art to produce the product by using the said process, the enablement requirement in "1.1.2.1.1 An Invention of a Product" should be referred to, if necessary. For instance, "1.1.2.1.1(2) 6) Deposit of microorganisms, etc." should be referred to if deposit of microorganisms, etc. is necessary.

Further, it is necessary to describe the industrial applicability of the said process or at least one use of the said product.

1.1.2.1.4 How Specifically the Detailed Description of the Invention Must Be Described?[3]

It is necessary for the applicant to describe at least one mode for showing how to carry out the claimed invention in the detailed description of the invention. When embodiments or working examples are necessary in order to explain the invention in such a way that a person skilled in the art can carry out the invention, "the mode for carrying out the invention" should be described in terms of embodiments or working examples. Embodiments or working examples are those which specifically show the mode for carrying out the invention (in case of an invention of a product, for instance, those which specifically show how to make the product, what structure it has, or how to use it, etc.)

In the case of inventions in technical fields where it is generally difficult to infer how to make and use a product on the basis of its structure, normally one or more representative embodiments or working examples are necessary which enable a person skilled in the art to carry out the invention.

---

[2] **(See Implementing Guidelines, Chapter 1-3.2.1(4).)**

[3] (See Implementing Guidelines, Chapter 1-3.2.1(5).)

Since this technical field (i.e., genetic engineering) is the one where it is difficult to infer how to make and use a product on the basis of its structure, normally one or more representative embodiments or working examples are necessary.

1.1.2.1.5 Balance of the Claim and the Detailed Description of the Invention[4]

In the detailed description of the invention, at least one mode for carrying out the invention needs to be described in terms of "claimed invention." For not all embodiments nor all alternatives within the extent (or the metes and bounds) of the claimed invention, the mode for carrying out the invention needs to be described.
However, when the examiner can show well-founded reasons that a person skilled in the art would be unable to extend the particular mode for carrying out the invention in the detailed description of the invention to the whole of the field within the extent (or the metes and bounds) of the claimed invention, the examiner should determine that the claimed invention is not described in such a manner sufficiently clear and complete to be carried out by a person skilled in the art. In such a case, the examiner should specifically point out a concrete reason and preferably the reason above should be supported by reference documents.

1.1.2.2 Ministerial Ordinance Requirement (See Implementing Guidelines, Chapter 1-3.3.)

Matters required under the Ministerial Ordinance are (1) technical field to which an invention pertains and (2) problem to be solved by the invention and its solution.

(1) Technical field to which an invention pertains

As "technical field to which an invention pertains," at least one technical field to which a claimed invention pertains shall be stated in a specification, in principle.
In the inventions of genetic engineering, "technical field to which an invention pertains" should be described such as pharmaceuticals, analytical agents, production of plants, for example.

(2) Problem to be solved by the invention and its solution

As "problem to be solved by the invention," an application shall state at least one technical problem to be solved by a claimed invention, in principle. As "its solution," an application shall explain how the technical problem has been solved by the claimed invention.
For example, in the case of the invention of the process for the production of a plant resistant to disease A by using a vector into which disease A-resistant gene B has been inserted, the problem to be solved by the invention should be described as "to produce a plant resistant to disease A" and the means for solving the problem should be described as "cloning disease-resistant gene B from the chromosomal DNA of another plant resistant to disease A, obtaining a recombinant vector inserted by the said gene, and regenerating the plant body from the plant cell transformed by the said vector."

1.1.2.3 Prior Art and Advantageous Effects (See Implementing Guidelines, Chapter 1-3.3.2(3).)

(1) Prior art

An applicant should describe background prior art, as far as he knows, which is deemed to contribute to understanding the technical significance of the claimed invention and examination of patentability of the invention, because such descriptions of prior art could teach the problem to be solved and could substitute the descriptions of the problems.
Also, documents related to prior art are one of the important means for evaluating the patentability of the claimed invention. Therefore, when there exist any documents relevant to the claimed invention, it is strongly recommended to cite such documents.

(2) Advantageous effects over prior art

It is an applicant's advantage to describe an advantageous effect of a claimed invention over the relevant prior art because such advantageous effect, if any, is taken into consideration as a fact to support to affirmatively infer the existence of an inventive step. Therefore, an applicant should describe an advantageous effect of a claimed invention over the relevant prior art, if any, as far as he knows.

[4] (See Implementing Guidelines, Chapter 1-3.2.1(6) and 3.2.3.)

1.1.3 Sequence Listing

(1) When a nucleotide sequence consisting of 10 or more nucleotides, or an amino acid sequence of a protein or peptide consisting of 4 or more L-amino acids is described in a specification, a "Sequence Listing" of the sequence prepared in accordance with "Guidelines for the preparation of specifications which contain nucleotide and/or amino acid sequence" published by the Public Notice of Japanese Patent Office should be described at the end of the detailed description of the invention as a part of it (See Note 15e of Form 29, Section 24 of Regulations under the Patent Law, and Note 12e of Form 14, Section 11 of Regulations under the Law concerning the Special Provisions to the Procedure, etc. relating to the Industrial Property Right). The "Sequence Listing" should be submitted in coding data.

(2) When a nucleotide sequence or an amino acid sequence is described in the scope of claim, the sequence described in the "Sequence Listing" prepared in accordance with "Guidelines for the preparation of specification which contain nucleotide and/or amino acid sequence" may be cited.

1.2 Unity of Invention
-applicable to applications filed on or after January 1, 1988-
(See Implementing Guidelines, Chapter 3-2.)

A single application may be filed for a set of claims describing inventions shown in the following examples.

[Example 1]
1) An invention of a chemical substance produced with the use of a transformant (referred to as the "specified invention")
2) An invention of a structural gene
3) An invention of a recombinant vector containing the structural gene; and
4) An invention of a transformant containing the structural gene

[Explanation]
A structural gene has an inherent function of determining the amino acid sequence of a specific chemical substance. Therefore, in providing the specific chemical substance, inventions of a structural gene, a recombinant vector containing the structural gene and a transformant containing the structural gene have a very close relationship with the chemical substance. Thus, since it may be considered that the inventions of the structural gene, the recombinant vector and the transformant provide means to obtain the specific chemical substance, these inventions and the invention of the chemical substance produced with the use of the transformant are considered to solve the same problem. Accordingly, the specified invention and inventions 2 to 4 above meet the relationship under Section 37(i) of the Patent Law.
In such a case, a claim directed to a process for producing the structural gene, the recombinant vector, or the transformant having the relationship provided in Section 37(iii) of the Patent Law with the inventions 2 to 4, for instance, may be included in a single application in accordance with the provision of Section 37(v) of the Patent Law.

[Example 2]
1) An invention of a parent cell (specified invention); and
2) An invention of a fused cell prepared from the parent cell

[Explanation]
Since a fused cell contains, in general, the characters of its parent cell as a part of its characters, the substantial part of the matters being to be stated in the claim of both inventions is considered to be the same. Accordingly, the specified invention and the invention 2 above meet the relationship under Section 37(ii) of the Patent Law.

[Example 3]
1) An invention of a transformant (specified invention)
2) An invention of a process for manufacturing a chemical substance using the transformant

[Explanation]
An invention of a process for producing a chemical substance using a transformant falls within the "invention directed to a process using the product" provided in Section 37(iii) of the Patent Law, because it utilizes functions and characteristics of the transformant.

[Example 4]
1) An invention of a gene (specified invention),
2) An invention of a process for producing a recombinant vector using the said gene; and
3) An invention of a process for producing a transformant using the said gene

[Explanation]
The invention 2 and invention 3 above fall within the "invention of a process using the product" under Section 37(iii) of the Patent Law, because it utilizes functions and characteristics of the gene.

[Example 5]
1) An invention of an antigenic protein (specified invention); and
2) An invention of a monoclonal antibody against the antigenic protein

[Explanation]
It is obvious that the above-mentioned protein is antigenic and an antigen is associated with a monoclonal antibody. An invention of the antigenic protein has a very close relationship with the monoclonal antibody in providing the monoclonal antibody against the antigenic protein. Since the invention of the antigenic protein is considered to aim at providing the monoclonal antibody against the antigenic protein, both inventions have the same problem to be solved. Accordingly, the specific invention and the invention 2 above fall within the relationship under Section 37(i) of the Patent Law.

However, the patent application does not meet the requirements of Section 37 of the Patent Law in the following case.

[Example 6]
1) An invention of a transformant (specified invention); and
2) An invention of a process using a chemical substance produced with the use of the transformant

[Explanation]
The specified invention and the invention 2 above do not fall within any of the relationships provided in Items of Section 37 of the Patent Law.
However, when a claim directed to the chemical substance produced with the use of the transformant is added, the invention 2 above has the relationship provided in Section 37(iii) of the Patent Law with the invention described in the added claim having the relationship provided in Section 37(i) of the Patent Law with the specified invention, and these inventions may be included in a single application in accordance with the provision of Section 37(v) of the Patent Law.

1.3 Requirements for Patentability

1.3.1 Invention Not Falling within "Industrially Applicable Invention"

Inventions of a gene, a vector, a recombinant vector, a transformant, a fused cell, a recombinant protein and a monoclonal antibody whose utility is not described in a specification or cannot be inferred, do not meet the requirements set forth in the first sentence in Section 29(1) of the Patent Law.

1.3.2 Novelty (See Implementing Guidelines, Chapter 2-1.)

(1) Recombinant protein

1) Where a protein X as an isolated and purified single substance is publicly known, a claimed invention concerning a recombinant protein X specified by a process of production, the said recombinant protein being identical as a chemical substance with the publicly known protein X, is not novel.

2) In case where a recombinant process inevitably leads to a different product, for example in its sugar chain or the like, due to the difference of the host cells, even though the recombinant protein has the same amino acid sequence as the publicly known one, a claimed invention concerning the recombinant protein specified by a process of production is novel.

(2) Monoclonal antibody

1) If antigen A is novel, a monoclonal antibody to the antigen A is generally considered novel. However, if a monoclonal antibody to publicly known antigen A' is publicly known and if the antigen A has the same epitope as that of A' because the antigen A is partially modified from publicly known antigen A' or the like, a monoclonal antibody to antigen A' also binds to antigen A. Therefore, in such a case, the claimed invention of "a monoclonal antibody to antigen A" is not novel.

2) The claimed invention of a monoclonal antibody specified by a cross-reactivity, such as "a monoclonal antibody which binds not to antigen B but to antigen A" is not novel, if a monoclonal antibody to antigen A is publicly known and if there is no particular technical significance to specify the monoclonal antibody described by such a cross-reactivity (e.g., when it is clear that the publicly known monoclonal antibody to antigen A does not bind to antigen B either, because antigen B has no similarities to antigen A in the function, structure, etc.).

1.3.3 Inventive Step (See Implementing Guidelines, Chapter 2-2.)

(1) Gene

1) An invention of a gene encoding Protein A has an inventive step, if Protein A has novelty and an inventive step.

2) Where Protein A is publicly known but its amino acid sequence is not publicly known, an invention of a gene encoding Protein A does not have an inventive step, provided that a person skilled in the art could determine the amino acid sequence easily at the time of filing. However, when it is considered that the gene is specified by a specific base sequence and has advantageous effects that a person skilled in the art cannot foresee in comparison with other genes having a different base sequence encoding the Protein A, the invention of the said gene has an inventive step.

3) When an amino acid sequence of Protein A is publicly known, an invention of a gene encoding the Protein A does not have an inventive step. However, when it is considered that the gene is specified by a specific base sequence and has advantageous effects that a person skilled in the art cannot foresee in comparison with other genes having a different base sequence encoding the Protein A, the invention of the said gene has an inventive step.

4) When a structural gene is publicly known, an invention relating to a structural gene of naturally obtainable mutant (allelic mutant, etc.) of the said publicly known structural gene and which is derived from the same species as the said structural gene and has the same properties and functions as the said structural gene does not have an inventive step. However, if the claimed structural gene has advantageous effects that a person skilled in the art cannot foreseen in comparison with the said publicly known structural gene, the claimed invention of the structural gene has an inventive step.

(2) Recombinant vector

In case where both a vector and a gene to be introduced are publicly known, a claimed invention concerning a recombinant vector obtained by a combination of them does not have an inventive step.
However, even if both a vector and a gene to be introduced are publicly known, a claimed invention concerning a recombinant vector with a specific combination of them, which leads to an advantageous effect that a person skilled in the art cannot foresee, has an inventive step.

(3) Transformant

If both a host and a gene to be introduced are publicly known, a claimed invention concerning the transformant obtained by a combination of them does not have an inventive step.
However, even if both of a host and a gene to be introduced are publicly known, a claimed invention concerning a transformant with a specific combination of them, which leads to an advantageous effect that a person skilled in the art cannot foresee, has an inventive step.

(4) Fused cell

If both of parent cells are publicly known, a claimed invention concerning a fused cell produced by fusing both of the parent cells does not have an inventive step. However, if the fused cell has advantageous effects that a person skilled in the art cannot foresee, the claimed invention of the fused cell has an inventive step.

(5) Monoclonal antibody

If antigen A is publicly known and it is clear that the antigen A has immunogenicity (for example, antigen A clearly has immunogenicity because a polyclonal antibody to the antigen A is publicly known or because the antigen A is a polypeptide with a large molecular weight, etc.), the claimed invention of "a monoclonal antibody to the antigen A " does not have an inventive step. However, if the claimed invention is further specified by other features, etc. which leads to an advantageous effect that a person skilled in the art cannot foresee, the claimed invention has an inventive step.

1.4 Amendment of Specification

Amendment of the specification relating to the deposit of microorganisms, etc. is handled as described in "2.3 Amendment of Specification" below.

2. Microorganisms

This section deals with inventions related to microorganisms per se as well as those related to the use of microorganisms, etc. Inventions relating to the use of microorganisms include not only those using a novel microorganism but also those based on finding of a method for using a publicly known microorganism (e.g., an invention of a process for producing a publicly known substance using a publicly known microorganism, an invention of a process for treating a material (e.g., water treatment, soil improvement) using a publicly known microorganism, an invention of use for a publicly known microorganism as a treating agent (e.g., water treating agent, soil improving agent).
The term "microorganisms" means yeasts, molds, mushrooms, bacteria, actinomyces, unicellular algae, virus, protozoa, etc. and further includes undifferentiated animal or plant cells as well as animal or plant tissue cultures.
Matters relating to genetic engineering are referred to "1. Genetic Engineering" even if they are inventions relating to microorganisms.

2.1 Description Requirements for the Specification

2.1.1 Designation of Microorganisms

In principle, microorganisms should be specified by scientific names in accordance with microbiological nomenclature. In case of designating a strain of a microorganism, it should be specified by the strain name following the species name (in accordance with microbiological nomenclature). When a microorganism cannot be specified by the species name, it may be specified by the strain name along with the genus name.
In case that a strain of a microorganism has been deposited, the said strain may be specified by the description of the accession number in addition to the species name or the strain name following the species name.

Example:
Bacillus subtilis FERM P-xxxxx strain

Undifferentiated animal or plant cells should be specified, in principle, by scientific names in accordance with zoological or botanical nomenclature or standard Japanese names, respectively.

2.1.2 Scope of Claim (See 1.1.1 above.)

According to Section 36(6)(ii) of the Patent Law, the invention for which a patent is sought shall be clear, therefore, scope of claim shall be described that an invention shall be clearly identified on the basis of statements of each claim.

2.1.3 The Detailed Description of the Invention (See 1.1.2 above.)

2.1.3.1 Enablement Requirement (See 1.1.2.1 above.)

2.1.3.1.1 An Invention of a Product (See 1.1.2.1.1 above.)

As to an invention of a product, a microorganism to be created or a microorganism to be used should be described as follows.

(1) A microorganism being explained clearly

In order to explain a microorganism clearly, the microorganism should be described as indicated below.

As to a new microorganism, the microorganism should be specified by the species name or the strain name following the species name in accordance with microbiological nomenclature, and also the microbiological characteristics should be described. As microbiological characteristics, it is desirable that taxonomic characteristics generally used in the field (Appendix 1) are described, however, other microbiological characteristics (e.g., selective productivity of metabolites) may be described.
A microorganism which cannot be specified by the species name should be specified by the strain name along with the genus name, after clarifying the reason why the species name cannot be specified.
Microbiological characteristics of a microorganism should be described as follows, depending on whether it is a new strain or a new species.

1) New strain

It should be clearly described that the characteristics of the strain as well as the difference in the microbiological characteristics of the strain from the publicly known strains within the same species to which the new strain belongs.

2) New species
The taxonomic characteristics of the species should be described in detail, and the reason why the microorganism is judged to be a new species should be clarified. That is, the difference of the species from the existing similar species should be expressly described, and the relevant literature used on the basis of the judgement should be indicated.

(2) "Can be made"

As to an invention relating to a microorganism per se or relating to the use of a novel microorganism, means for creating the microorganism should be described so that a person skilled in the art can create the said microorganism. Means for creating microorganisms includes means for screening, means for mutagenesis, means for gene recombination, etc.
If the means for creating the microorganism cannot be described in the detailed description of the invention so that a person skilled in the art can create the said microorganism, it is necessary to deposit the microorganism in accordance with Section 27bis of Regulations under the Patent Law (the detail is as follows).

1) Deposit and Furnishing of Microorganisms

Section 27bis of Regulations under the Patent Law (Deposition of microorganisms)
1 A person desiring to file a patent application for an invention involving or using a microorganism shall attach to the request a copy of the latest receipt referred to in Rule 7 of the Regulations under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the purpose of Patent Procedure (hereinafter referred to as "Treaty") for the deposit of the microorganism issued by the international depositary authority defined in Article 2(viii) of the Treaty, or a document certifying the fact that the microorganism has been deposited with an institution designated by the Commissioner of the Patent Office, except where the microorganism is readily available to a person skilled in the art to which the invention pertains.
2 Where an accession number is newly given after the filing of a patent application to the deposit of a microorganism under the preceding paragraph, the applicant for a patent or the patentee shall notify the Commissioner of the Patent Office without delay.
3 The notification under the preceding paragraph shall be made in accordance with Form 32 with respect to a patent application, or Form 33 with respect to an International Patent Application.

Section 27ter of Regulations under the Patent Law (Furnishing of microbiological samples)
1 A person who intends to work for the purpose of tests or experiments an invention involving or using a microorganism deposited in accordance with the preceding section may be furnished with a sample of the microorganism provided that:
(i) registration for the establishment of a patent right to the invention involving or using the microorganism has been made;
(ii) the person received a warning given in the form of a document describing the contents of the invention involving or using the microorganism in accordance with Section 65(1) of the Patent Law; or
(iii) such is necessary in order to prepare a written argument referred to in Section 50 of the Patent Law (including its application under Section 159(2) (including its application under Section 174(2)) and Section 163(2)).
2 A person who has been furnished with a sample of the microorganism in accordance with the preceding paragraph shall not permit a third party to utilize the sample of the microorganism.

(i) A person desiring to file a patent application for an invention involving or using a microorganism, shall deposit the microorganism with a depositary institution designated by the Commissioner of the Patent Office or international depositary authorities (hereinafter, the both are referred to as "depositary institution for the purposes of patent procedure"), unless a person skilled in the art can easily obtain the microorganism, shall state the accession number in the specification as filed, and shall attach to the request a document certifying the fact that the microorganism has been deposited.
When a new accession number is given to the microorganism after filing, for the reason that, e.g., re-deposit was made, samples of the microorganism were transferred to another international depositary authority, or the deposit was converted from the deposit under the national law to that under the Budapest Treaty, the applicant or the patentee shall give a notice to that effect to the Commissioner of the Patent Office without delay.
Where a microorganism which was deposited with a depositary institution designated by the Commissioner of the Patent Office and was confirmed to be viable is found to be no longer viable, the depositor, upon receipt of the "Notice that the microorganism cannot be furnished" (Official Gazette of MITI No.178 Section 15) from the depositary institution, should deposit immediately the same microorganism as that originally deposited. Where the

microorganism is related to a patent application or a patent, the applicant or the patentee should give a notice to that effect to the Commissioner of the Patent Office without delay. In such a case, the newly deposited microorganism is treated as having been deposited without intermission since the original deposit was made.
The deposited microorganism can be furnished simultaneously with the registration for establishment of a patent right. Even prior to the registration for establishment of a patent right, though, in the case where Section 27ter (1)(ii) or (iii) of Regulations under the Patent Law is applied, the microorganism can be furnished.
The deposit of a microorganism should be maintained at least during the term of the patent for the invention related to the microorganism so that the microorganism can be furnished.

For reference, a list of International Depositary Authorities and kinds of microorganisms accepted by the IDAs is shown in Appendix 2.

(ii) Microorganisms excluded from obligation to be deposited

(a) Microorganisms which cannot be stored or maintained by the depositary institution for the purpose of patent procedure for technical reasons or the like

In such a case, however, furnishing of the microorganisms provided in Section 27ter of Regulations under the Patent Law should be guaranteed by the applicant. (Such microorganisms should be preferably deposited with a reliable cultural collection.)

(b) Microorganisms readily available to the persons skilled in the art stated in "Section 27bis of Regulations under the Patent Law"
More specifically, the following microorganisms are included for example:
(b-1) Commercially available microorganisms, such as baker's yeast, koji (Aspergillus oryzae), Bacillus natto, etc.
(b-2) A stored microorganism in the case where it has been confirmed, prior to filing, that the microorganism has been stored at a reliable cultural collection and is freely accessible from a catalog or the like issued by the said cultural collection
In this case, the storage number of the microorganism should be described in the specification as filed.
(b-3) Microorganisms which can be created by a person skilled in the art on the basis of the description in the specification

(iii) Where a claimed invention in an application claiming priority relates to a microorganism which is not readily available to a person skilled in the art, the application can enjoy advantages of the priority provided that the microorganism has been deposited with a depositary institution for the purpose of patent procedure or a reliable public cultural collection and that the accession number or storage number of the microorganism is stated in the specification contained in the first application which has served as a basis for claiming a right of priority or in the specification contained in the earlier application which has served as a basis for claiming a right of internal priority.

(3) "Can be used"

For the invention of a microorganism per se or of the use of a microorganism, in order to show the industrial applicability of it, the way of industrial application of the product shall be described in the detailed description of the invention except where it could be understood by a person skilled in the art without such description when taking into account the overall descriptions of the specification (excluding claims), drawings and common general knowledge as of the filing.

2.1.3.1.2 An Invention of a Process (See Implementing Guidelines, Chapter 1-3.2.1 (3).)

Of those inventions related to the use of a microorganism, an invention of a process for the use of a microorganism (e.g. an invention of a process for treating a material with a microorganism) should be described as follows.
For an invention of a process, the definition of carrying out the invention is to use the process and that a process can be used is interpreted as meaning that a process can be used in an industrially applicable way. Further, "the said invention of a process" should be explained clearly in the detailed description of the invention.
Accordingly, for the invention of a process for the use of microorganism, in order to show the industrial applicability of it, the way of industrial application of the process shall be described in the detailed description of the invention except where it could be understood by a person skilled in the art without such description when taking into account the overall descriptions of the specification (excluding claims), drawings and common general knowledge as of the filing. In order to describe the industrial applications, the enablement requirement described in

"2.1.3.1.1 An Invention of a Product" should be referred to, if necessary. For instance, "2.1.3.1.1 An Invention of a Product (2) Deposit and furnishing of microorganisms" should be referred to, if the deposit of microorganisms is necessary.

2.1.3.1.3 An Invention of a Process for Manufacturing a Product (See Implementing Guidelines, Chapter 1-3.2.1(4).)

Of those inventions related to the use of a microorganism, an invention of a process for producing a substance using a microorganism should be described as follows.
Where an invention of a process is directed to "a process for manufacturing a product," the definition of "the process can be used" means that the product can be manufactured by the process and either the process or the product shall be industrially applicable to meet industrial application. Further, the said invention of a process for manufacturing a product should be explained clearly in the detailed description of the invention.
Accordingly, for the invention of a process for producing a substance by using a microorganism, a process for producing the said substance shall be described in the detailed description of the invention so that a person skilled in the art can produce the said substance taking into account the overall descriptions of the specification (excluding claims), drawings and common general knowledge as of the filing. In order to describe the process in such a manner that a person skilled in the art can produce the said substance by the process, the enablement requirement described in "2.1.3.1.1 An Invention of a Product" should be referred to, if necessary. For instance, "2.1.3.1.1 An Invention of a Product (2) Deposit and furnishing of microorganisms" should be referred to, if the deposit of microorganisms is necessary.
Further, it is necessary to describe the industrial applicability of the said process or at least one use of the said substance.

As to "How Specifically the Detailed Description of the Invention Must Be Described?" and "Balance of the Claim and the Detailed Description of the Invention," see the relevant portions (1.1.2.1.4 and 1.1.2.1.5) in "1. Genetic Engineering."

2.1.3.2 Ministerial Ordinance Requirement (See 1.1.2.2 above.)

Matters required under the Ministerial Ordinance are (1) technical field to which an invention pertains and (2) problem to be solved by the invention and its solution.

(1) Technical field to which an invention pertains

As "technical field to which an invention pertains," at least one technical field to which a claimed invention pertains shall be stated in a specification, in principle.
In the inventions related to a microorganism, "technical field to which an invention pertains" should be described such as pharmaceuticals, feed, food, water treatment, for example.

(2) Problem to be solved by the invention and its solution

As "problem to be solved by the invention," an application shall state at least one technical problem to be solved by a claimed invention, in principle. As "its solution," an application shall explain how the technical problem has been solved by the claimed invention.

As to "Prior Art and Advantageous Effects," see 1.1.2.3 in "1. Genetic Engineering."

2.2 Requirements for Patentability

2.2.1 Invention Not Falling within "Industrially Applicable Invention"
The following inventions do not meet the requirement provided in the first sentence in Section 29(1) of the Patent Law.

(1) A mere discovery which is not a creation
Example: A merely discovered microorganism existing in nature.
However, an invention of a microorganism which is isolated from nature artificially involves creativity.

(2) Inventions incapable of industrial application

An invention of a microorganism per se whose utility is not described or cannot be inferred.

2.2.2 Inventive Step (See Implementing Guidelines, Chapter 2-2.)

(1) Invention of a microorganism per se

An inventive step of an invention of a microorganism per se should be examined based on taxonomic characteristics of the microorganism as well as effects produced by the use of the microorganism.

1) An invention of a microorganism whose taxonomic characteristics are remarkably different from those of publicly known species (i.e., a new species) has an inventive step.

2) An invention involving a microorganism producing advantageous effects that a person skilled in the art cannot foresee, though the taxonomic characteristics of the microorganism are not substantially different from those of publicly known species, has an inventive step.
Example:
A microorganism which was obtained by mutating a publicly known species and which has remarkably high productivity of metabolite.

(2) Invention relating to the use of a microorganism

1) An invention relating to the use of a microorganism (e.g., an invention of a process for producing a substance) does not have an inventive step, if the microorganism used in the invention is a taxonomically known species and belongs to the same genus as another microorganism for which the same mode of use (e.g., producing the aimed substance) is known. However, if it is found that the invention using the former microorganism has advantageous effects that a person skilled in the art cannot foresee in comparison with the invention using the latter microorganism, the invention using the former microorganism has an inventive step.

(Explanation)
Between publicly known species in the same genus, it is usually easy for a person skilled in the art to culture each microorganism and confirm its utility (e.g., substance productivity) and its effects.

2) An invention relating to the use of a microorganism (e.g., an invention of a process for producing a substance) has an inventive step, if the microorganism used in the invention is remarkably different from publicly known species in taxonomic characteristics (i.e., a new species), even if the mode of use (e.g., the aimed substance) is the same.

(Explanation)
Since the used microorganism per se has an inventive step as described (1) 1) above, a process using the microorganism has also an inventive step.

2.3 Amendment of Specification
- applicable to applications filed on or after January 1, 1994 -
(See "Implementing Guidelines for Amendment of Specification and Drawings" (Nov. 1993, the Japanese Patent Office) Chapter 1-1.)

(1) An amendment of an accession number of a microorganism is not regarded as addition of a new matter, where microbiological characteristics of the microorganism are described to the extent that the microorganism can be specified in the specification as filed and deposit of the microorganism can be specified based on the name of the depositary institution, etc.
In such a case, the applicant should make an amendment of the accession number without delay.

(2) An amendment converting a storage number of a microorganism to an accession number based on the deposit of the microorganism with a depositary institution for the purpose of patent procedure is not regarded as addition of a new matter, where the microorganism used is stored at a reliable public cultural collection and the storage number of the microorganism is explicitly stated in the specification as filed and that it is clear that the identity of the microorganism is not lost.
In such a case, the applicant should make an amendment of the accession number without delay.

(3) An amendment adding microbiological characteristics of a microorganism is regarded as addition of a new matter unless a person skilled in the art can directly and unambiguously derive those characteristics from what is described in the specification and drawings as filed, even if the accession number of the microorganism stated in the

specification as filed is not changed and microbiological characteristics of the microorganism are described in the specification as filed to the extent that the taxonomic species of the microorganism can be specified.

3. Plants

This section deals with inventions of plants per se, those relating to parts of plants (e.g., a fruit), those of a process for creating plants, those relating to use of plants, etc. The term "plants" means the plants under the classification where organisms are classified into three groups, namely microorganisms, plants and animals.
As to undifferentiated plant cells as well as plant tissue cultures, which are treated as microorganisms, reference should be made to relevant parts in "2. Microorganisms."
Matters relating to genetic engineering are referred to "1. Genetic Engineering" even if they are inventions relating to plants.

3.1 Description Requirements for the Specification

3.1.1 Designation of Plants

In principle, plants should be specified by scientific names in accordance with the botanical nomenclature or standard Japanese names.

3.1.2 Scope of Claim (See 1.1.1 above.)

As to an invention relating to a plant, a claim should be described as follows.

In the case of an invention of a plant per se, the plant should be specified by, for example, a combination of any of the species, the distinctive gene of the plant, characteristics of the plant, etc. and may be further specified by the process for creating the plants.

Example 1:
A plant belonging to Castanea crenata (Japanese chestnut) having the ATCC Accession No.
xxxx whose bark contains catechol tannin and pyrogallol tannin in the ratio of X_1 -X_2 : Y_1 -Y_2 and has a catechol tannin content of z_1 -z_2 ppm (weight ratio), or its mutatnt having the said characteristics.

Example 2:
A watermelon obtained by crossing a diploid watermelon with a tetraploid watermelonobtained by polyploidizing a diploid watermelon, whose somatic cell has 33 chromosomes.

As to an invention of a process for creating a plant, the process for creating the plant should be described in the claim step by step. In the case where selection is performed as one step of creation based on characteristics or the like, the characteristics or the like necessary for the selection should be additionally described. Where conditions such as environment are necessary for creating the plant, such conditions should be also described.

Example:
A process for creating a cabbage characterized by crossing a cabbage strain having the
ATCC Accession No.xxxx as a seed parent with another cabbage as a pollen parent by having resistance for the herbicide X.

3.1.3 The Detailed Description of the Invention (See 1.1.2 above.)

As to an invention of a plant per se or that of a process for creating a plant, the detailed description of the invention should be described as follows.

3.1.3.1 Enablement Requirement (See 1.1.2.1 above.)

3.1.3.1.1 An Invention of a Product (See 1.1.2.1.1 above.)

An invention of a plant per se should be described as follows.

(1) A plant being explained clearly

In order to explain a plant clearly, for example, 1) matters regarding species of the plant created and 2) matters relating to characteristic properties of the created plant should be described.

1) Species of the plant created

In principle, the created plant should be specified by the scientific name in accordance with the botanical nomenclature or standard Japanese name.

2) Characteristic properties of the plant created

In the case that properties of the created plant are characteristic, they should be described specifically stating by numeric values actually obtained by measuring or the like and it is desirable that they are described in comparison with those of publicly known plants, if necessary.
For instance, it should be described not by a mere statement that the plant is high-yielding, but concrete numeric values commonly used in conventional yield surveys, such as total number of fruits produced per stock, total weight of fruits produced per stock, gross yield per are, etc., and they should be described in comparison with those of publicly known plants, if necessary.
Colors, such as leaf color, fruit color, and flower color should be expressed in accordance with official standards, such as the color atlas JIS Z8721 which is a specification of colours according to their three attributes, JIS Z8102 concerning color names and the R.H.S. color chart.
Where characteristic properties of the created plant cannot be expressed by a conventional cultivation method which a person skilled in the art usually conducts, or where characteristic properties of the created plant are expressed only in specific environments and under specific cultivation method though the method is conventional, such specific cultivation conditions should be specifically described.

(2) "Can be made"

As to an invention of a plant per se, a process for creating the plant should be described step by step including species of parent plant(s), a step of selecting the plant to be aimed at based on objective indicators or the like.

(a) Where a person skilled in the art cannot carry out the invention because of unavailability of the parent plant(s) even if the process for creating the plant is described in the specification step by step, its parent plant(s) (seeds, cells, etc.) should be deposited with a depositary institution prior to filing and its accession number should be described in a specification as filed similarly to the deposit under Section 27bis of Regulations under the Patent Law.

(b) Where it is not possible to describe a process for creating the plant in the specification in such a manner that enables a person skilled in the art to create the plant, the created plant which is reproducible (seeds, cells, etc.) should be deposited with a depositary institution prior to filing and its accession number should be described in a specification as filed similarly to the deposit under Section 27bis of Regulations under the Patent Law.

However, where the above-mentioned plant cannot be deposited with the depositary institute for the purpose of patent procedure due to some technical reasons or the like, means for obtaining the above should be described in the specification and the applicant should guarantee the furnishing of the samples similarly to the furnishing of samples under Section 27ter of Regulations under the Patent Law. (Such a plant should be preferably deposited with a reliable cultural collection.)

For the details of the deposit and furnishing of microorganisms, etc., see "2.1.3.1.1 (2) Deposit and Furnishing of Microorganisms in 2. Microorganisms"

(3) "Can be used"

For an invention of a plant per se, in order to show the industrial applicability of it, the way of industrial application of the product shall be described in the detailed description of the invention except where it could be understood by a person skilled in the art without such description when taking into account the overall descriptions of the specification (excluding claims), drawings and common general knowledge as of the filing.

3.1.3.1.2 An Invention of a Process for Manufacturing a Product (See 1.1.2.1.3 above.)

An invention of a process for creating a plant should be described as follows.
An invention of a process for creating a plant should be described in such a manner that enables a person skilled in the art to create the plant by the said process.

In order to describe the process in such a manner that a person skilled in the art can produce the said plant by the process, the enablement requirement described in "3.1.3.1.1 An Invention of a Product" should be referred to, if necessary. For example, in case that deposit of a plant is necessary, "3.1.3.1.1 (2) Can be made" should be referred to.

Further, in an invention of a process for creating a plant, how the process or the plant created by the process is industrially applicable should be described in the detailed description of the invention, except where it could be understood by a person skilled in the art without such description when taking into account the overall descriptions of the specification (excluding claims), drawings and common general knowledge as of the filing.

As to "How Specifically the Detailed Description of the Invention Must Be Described?", "Balance of the Claim and the Detailed Description of the Invention," " Ministerial Ordinance Requirement" and "Prior Art and Advantageous Effects," see the relevant portions (1.1.2.1.4, 1.1.2.1.5, 1.1.2.2 and 1.1.2.3) in "1. Genetic Engineering."

3.1.4 Drawings

When photographs are attached as drawings, black-and-white photographs should be used. Color photographs may be submitted as reference materials.

3.2 Requirements for Patentability

3.2.1 Invention Not Falling within "Industrially Applicable Invention"

The following inventions do not meet the requirement provided in the first sentence in Section 29(1) of the Patent Law.

(1) Mere discovery which is not a creation

Mere recognition of a plant existing in nature as it is does not involve creativity and is nothing but a discovery. Example: A newly discovered plant per se.

In order to show that an invention involves creativity, how the invention has been created should be described in the detailed description of the invention.

(2) Inventions incapable of industrial application

Inventions whose utility is not described or cannot be inferred.

3.2.2 Inventive Step

(1) An invention of a plant per se does not have an inventive step, where characteristics of the plant created can be easily predicted from the characteristics of publicly known plants within the species to which the plant belongs and where the invention does not have advantageous effects that a person skilled in the art cannot foresee.

Example 1:
A plant whose shape or color is similar to that of publicly known plants within the species to which the plant belongs.
Example 2:
Mere combination of the characteristics of publicly known plants within the species to which the plant belongs. (Plants obtained by mere crossing: for instance, suppose that it is publicly known that Pisum sativum A (pea A) has a single-locus-controlling characteristics that the legume is yellow when premature and Pisum sativum B has a single-locus-controlling characteristics that it bears blossoms at each knot through the full length. In such a case, a new Pisum sativum, obtained by merely crossing Pisum sativum A and Pisum sativum B and fixing their characteristics, having characteristics that the legume is yellow when premature and it bears blossoms at each knot, does not have an inventive step.)

(2) An invention of a process for creating a plant does not have an inventive step, where the selection of parent plants, means, conditions or the like is not considered to be difficult and where the created plant does not have advantageous effects that a person skilled in the art cannot foresee.

3.3 Amendment of Specification

Amendment of the specification relating to the deposit of plants is handled as described in "2.3 Amendment of Specification" above.

4. Animals

This section deals with inventions of animals per se, those relating to parts of animals, those of a process for creating animals, those relating to use of animals, etc. The term "animals" means the animals (excluding humans) under the classification where organisms are classified into three groups, namely microorganisms, plants and animals.
As to undifferentiated animal cells as well as animal tissue cultures, which are treated as microorganisms, reference should be made to relevant parts in "2. Microorganisms."
Matters relating to genetic engineering are referred to "1. Genetic Engineering" even if they are inventions relating to animals.

4.1 Description Requirements for the Specification

4.1.1 Designation of Animals

In principle, animals should be specified by scientific names in accordance with the zoological nomenclature or standard Japanese names.

4.1.2 Scope of Claim (See 1.1.1 above.)

As to an invention relating to an animal, a claim should be described as follows.

In the case of an invention of an animal per se, the animal should be specified by, for example, a combination of any of the species, the distinctive gene of the animal, characteristics of the animal, etc. and may be further specified by the process for creating the animals.

Example:
A mouse having DSM Accession No.xxxxx characterized by the occurrence of degeneration and swelling of anterior lens cortical fibers at 8 weeks of age, appearance of opacity of the lens at 5 or 6 months of age and rapid completion of cataract immediately after that, or its mutant having the said characteristics.

As to an invention of a process for creating an animal, the process for creating the animal should be described in the claim step by step. In the case where selection is performed as one step of creation based on characteristics or the like, the characteristics or the like necessary for the selection should be additionally described. Where conditions such as environment are necessary for creating the animal, such conditions should be described.

4.1.3 The Detailed Description of the Invention (See 1.1.2 above.)

As to an invention of an animal per se or that of a process for creating animals, the detailed description of the invention should be described as follows.

4.1.3.1 Enablement Requirement (See 1.1.2.1 above.)

4.1.3.1.1 An Invention of a Product (See 1.1.2.1.1 above.)

An invention of an animal per se should be described as follows.

(1) An animal being explained clearly

In order to explain an animal clearly, for example, 1) matters regarding species of the animal created and 2) matters relating to characteristic properties of the created animal should be described.

1) Species of the animal created

In principle, the created animal should be specified by the scientific name in accordance with the zoological nomenclature or standard Japanese name.

2) Characteristic properties of the animal created

In the case that properties of the created animal are characteristic, they should be described specifically stating by numeric values actually obtained by measuring or the like and it is desirable that they are described in comparison with those of publicly known animals, if necessary.
Where characteristic properties of the created animal cannot be expressed by a conventional breeding method which a person skilled in the art usually conducts and they are expressed only in specific environments or only under specific breeding method, such specific conditions should be specifically described.

(2) "Can be made"

As to an invention of an animal per se, the process for creating the animal should be described step by step including species of parent animal(s), a step of selecting an animal to be aimed at based on objective indicators or the like.

(a) Where a person skilled in the art cannot carry out the invention because of unavailability of the parent animal(s) even if the process of creating the animal is described in the specification step by step, its parent animal(s) (fertilized ovum, etc.) should be deposited with a depositary institution prior to filing and its accession number should be described in a specification as filed similarly to the deposit under Section 27bis of Regulations under the Patent Law.

(b) Where it is not possible to describe the process for creating the animal in the specification in such a manner that enables a person skilled in the art to create the animal, the created animal which is reproducible (fertilized ovum, etc) should be deposited with a depositary institution prior to filing and its accession number should be described in a specification as filed similarly to the deposit under Section 27bis of Regulations under the Patent Law.

However, where the above-mentioned animal cannot be deposited with the depositary institute for the purpose of patent procedure due to some technical reasons or the like, means for obtaining the above should be described in the specification and the applicant should guarantee the furnishing of the samples similarly to the furnishing of samples under Section 27ter of Regulations under the Patent Law. (Such an animal should be preferably deposited with a reliable cultural collection.)

For the details of the deposit and furnishing of microorganisms etc., see "2.1.3.1.1 (2) Deposit and Furnishing of Microorganisms in 2. Microorganisms"

(3) "Can be used"

For an invention of an animal per se, in order to show the industrial applicability of it, the way of industrial application of the product shall be described in the detailed description of the invention except where it could be understood by a person skilled in the art without such description when taking into account the overall descriptions of the specification (excluding claims), drawings and common general knowledge as of the filing.

4.1.3.1.2 An invention of a Process for Manufacturing a Product (See 1.1.2.1.3 above.)

An invention of a process for creating an animal should be described as follows.
An invention of a process for creating an animal should be described in such a manner that enables a person skilled in the art to create the animal by the said process.

In order to describe the process in such a manner that a person skilled in the art can produce the said animal by the process, the enablement requirement described in "4.1.3.1.1 An Invention of a Product" should be referred to, if necessary. For example, in case that deposit of an animal is necessary, "4.1.3.1.1 (2) Can be made " should be referred to.

Further, in an invention of a process for creating an animal, how the process or the animal created by the process is industrially applicable should be described in the detailed description of the invention, except where it could be understood by a person skilled in the art without such description when taking into account the overall descriptions of the specification (excluding claims), drawings and common general knowledge as of the filing.

As to "How Specifically the Detailed Description of the Invention Must Be Described?", "Balance of the Claim and the Detailed Description of the Invention," " Ministerial Ordinance Requirement" and "Prior Art and Advantageous Effects," see the relevant portions (1.1.2.1.4, 1.1.2.1.5, 1.1.2.2 and 1.1.2.3) in "1. Genetic Engineering."

4.1.4 Drawings

When photographs are attached as drawings, black-and-white photographs should be used. Color photographs may be submitted as reference materials.

4.2 Requirements for Patentability

4.2.1 Invention Not Falling within "Industrially Applicable Invention"

The following inventions do not meet the requirement provided in the first sentence in Section 29(1) of the Patent Law.

(1) Mere discovery which is not a creation

Mere recognition of an animal existing in nature as it is does not involve creativity and is nothing but a discovery. Example: A newly discovered bird per se.

In order to show that an invention involves creativity, how the invention has been created should be described in the detailed description of the invention.

(2) Inventions incapable of industrial application

Inventions whose utility is not described or cannot be inferred.

4.2.2 Invention Contravening Public Order, Morality or Public Health

When working of an invention inevitably contravenes public order, morality or public health, the invention falls under the invention as provided in Section 32 of the Patent Law.

4.2.3 Inventive Step (See Implementing Guidelines, Chapter 2-2.)

(1) An invention of an animal per se does not have an inventive step, where characteristics of the animal created can be easily predicted from the characteristics of publicly known animals within the species to which the animal belongs and where the invention does not have advantageous effects that a person skilled in the art cannot foresee.

(2) An invention of a process for creating an animal does not have an inventive step, where the selection of parent animal(s), means, conditions or the like is not considered to be difficult and where the created animal does not have advantageous effects that a person skilled in the art cannot foresee.

4.3 Amendment of Specification

Amendment of the specification relating to the deposit of animals is handled as described in "2.3 Amendment of Specification" above.

Appendix 1:
The Guidelines for Describing Taxonomic Characters

Appendix 2:
The List of International Depositary Authorities and Kinds of Microorganisms Accepted by the IDAs

[Reference]

The application of these guidelines should be as follows.

1. Genetic Engineering

(i) New practices under the 1994-Revised Japanese Patent Law to be applicable to applications filed on and after July 1, 1995.

1.1 Description Requirements for Specification
1.1.1 Scope of Claim
1.1.2 The Detailed Description of the Invention (1.1.2.2 Ministerial OrdinanceRequirement)

(ii) Clarification of the ambiguity of some current practices to be applicable to all pending applications.

1.1 Description Requirements for Specification
1.1.2 Description of the Invention (1.1.2.1 Enablement Requirement)
1.1.3 Sequence Listing
1.2 Unity of Invention
1.3 Requirements for Patentability

2. Microorganisms

Ditto

3. Plants

Ditto

4. Animals

Ditto

Examples of examinations on the inventions related to genes (DNA fragments, full-length cDNAs, and Single Nucleotide Polymorphisms)" (abridged translation)

The original version of the "Examples of examinations on the inventions related to genes (DNA fragments, full-length cDNAs, and Single Nucleotide Polymorphisms)" is available from the JPO homepage. When any ambiguity of interpretation is found in this translation, the Japanese original text shall prevail.

[Contact us]
Examination Standards Office,
First Patent Examination Department,
Japan Patent Office,
3-4-3 Kasumigaseki, Chiyoda-ku, Tokyo 100-8915, JAPAN
F a x: +81-3-3597-7755
E-mail: pa2a12@jpo.go.jp

1. Unity of Invention
Case 1 (Unity of Invention : No) DNA fragments
Case 2 (Unity of Invention : Yes) DNA fragments

2. Enablement Requirement: No
Case 3 Full-length cDNA
Case 4 Full-length cDNA

Case 5 Full-length cDNA

3. Inventive Step: No
Case 6 Full-length cDNA

4. Inventive Step: No, Enablement Requirement : No
Case 7 DNA fragment
Case 8 SNPs

5. Inventive Step: Yes, Enablement Requirement : Yes
Case 9 DNA fragment
Case 10 Full-length cDNA
Case 11 SNP

1. Unity of Invention

Case 1 DNA fragments (Unity of invention: no)

Claims

1. A polynucleotide consisting of the nucleotide sequence of SEQ ID NO:1.
2. A polynucleotide consisting of the nucleotide sequence of SEQ ID NO:2.

Description of the invention

Both of the claimed 500bp polynucleotides were derived from the same cDNA library constructed from human liver. Both of the claimed polynucleotides are part of structural genes, and they can be used as probes in one of the steps to obtain the full-length DNAs. The nucleotide sequence of SEQ ID NO:1 showed 5% homology to the nucleotide sequence of SEQ ID NO:2.

Result of the prior-art search

The nucleotides derived from human liver are known.

Reason for rejection (Unity of invention)

As there are so many known polynucleotides derived from human liver, the mere fact that these DNA sequences have the same source does not mean that these sequences have the same technical problem to be solved because the technical problem must be the one which is unsolved before the filing.

Furthermore, it cannot be said that substantial parts of the matters stated in the claims are the same since the nucleotide sequence of SEQ ID NO:1 showed 5% homology to the nucleotide sequence of SEQ ID NO:2.

In this case, therefore, unity of invention cannot be acknowledged.

(Attention)

If the application does not comply with the requirement of unity of invention, the invention set forth in the first claim (and those inventions having unity with the said invention) should be examined in respect of other requirements (novelty, inventive step, enablement requirement, etc.)

Please refer to the case 7 in respect of other requirements.

Case 2 DNA fragments (Unity of Invention: yes)

Claims
1. A polynucleotide consisting of the nucleotide sequence of SEQ ID NO:3.
2. A polynucleotide consisting of the nucleotide sequence of SEQ ID NO:4.

Description of the invention
These polynucleotides are the 500bp cDNAs which were found in cDNA library derived from hepatocyte of patients with disease Y but not found in those of normal persons. It was confirmed by northern hybridization that the corresponding mRNAs were expressed only in the patients' hepatocyte.
Therefore, these polynucleotides can be used as probes to diagnose disease Y. The nucleotide sequence of SEQ ID NO:3 showed 5% homology to the nucleotide sequence of SEQ ID NO:4.

Result of the prior-art search
There is no known polynucleotide or protein which are unique in the patients with disease Y.

Reason for rejection (unity of invention)
No reason for rejection

(Attention)
Since both of the claimed inventions are related to specific DNAs in the patients with disease Y, the field of industrial application is considered to be the same. And both of the claimed inventions have the same problem to be solved that they provide for the first time multiple group of polynucleotides which are specific to patients with disease Y because no such DNA was known before the time of filing. Therefore, these claims have unity of invention.

Please refer to case 9 in respect of other requirements.

2. Enablement Requirement :No

Case 3 Full-length cDNA

Claim 1
A polynucleotide consisting of the nucleotide sequence of SEQ ID NO: 5.

Description of the invention
The claimed polynucleotide is 3000bp cDNA obtained from human liver cDNA library. It encodes a polypeptide of amino acid sequence of SEQ ID NO:6. As a result of similarity search, no known sequences showed over 30% similarity to the nucleotide sequence of SEQ ID NO:5 or the amino acid sequence of SEQ ID NO:6. The amino acid sequence of SEQ ID NO:6 was proved to have a potential site of glycosylation.

Therefore, the claimed polynucleotide is assumed to be a structural gene encoding a new glycoprotein, whose specific function is unknown, and may be used for obtaining a new drug.

Result of the prior-art search

There is no known nucleotide sequence with over 30% similarity to that of SEQ ID NO:5.
There is no known amino acid sequence with over 30% similarity to that of SEQ ID NO:6.

Reason for rejection

Even if the claimed polynucleotide encodes glycoprotein, the corresponding glycoprotein's specific function cannot be recognized because there are so many glycoproteins whose specific function differs from each other. The specific function of the claimed polynucleotide also cannot be assumed with the common general knowledge. As the specific function of the claimed polynucleotide is not clear, it is not clear how to use the claimed polynucleotide.
Therefore, there is no disclosure concerning the use of the claimed polynucleotide, thus, the description of the invention is deemed insufficient for enabling a person skilled in the art to carry out the invention.

(Attention)
The above mentioned reason for rejection normally shall not be overcome.

Case 4 Full-length cDNA

Claim 1

A polynucleotide consisting of the nucleotide sequence of SEQ ID NO:7.

Description of the invention

The claimed polynucleotide is 2400bp cDNA obtained from human liver cDNA library. It encodes a polypeptide of 800 amino acids of SEQ ID NO.8. As a result of similarity search using a known DNA and amino acid database, the claimed polynucleotide showed 20 to 30% homology to the polynucleotides encoding factor WW1 of mammalians such as rats. The polynucleotides are written in document A, document B, etc. And the amino acid sequence of SEQ ID NO.8 showed 20 to 30% homology to the amino acid sequences of factor WW1 of mammalians such as rats. The amino acid sequences are also written in document A, document B, etc.

Therefore, the claimed polynucleotide was assumed to encode human factor WW1 and to be useful.

Result of the prior-art search

There is no known sequence with over 40% similarity to the nucleotide sequence of SEQ ID NO:7 or the amino acid sequence of SEQ ID NO:8.

Reason for rejection

The given reason by the applicant that this polynucleotide encodes human factor WW1 is only based on the fact that the claimed polynucleotide has 20 to 30% homology to other mammalian polynucleotides encoding factor WW1 and that the amino acid sequence of SEQ ID NO:8 has 20 to 30% homology to amino acid sequences of factor WW1 of other mammalians.

In general, when two polynucleotides (polypeptides) show only 20-30% homology to each other, they probably do not have any specific function in common. And there is no common general knowledge that the human polynucleotide, with only 20-30% homology to the polynucleotide of factor WW1, encodes human factor WW1. As the claimed polynucleotide probably does not

encode human factor WW1, the specific function of the claimed nucleotide is not clear and no one can assume the specific function of the protein encoded by the nucleotide.

Therefore, we consider there is no disclosure concerning the use of this polynucleotide in an industrial applicable way, thus the description of the invention is deemed insufficient for enabling a person skilled in the art to carry out the invention.

(Attention)
If the claimed polynucleotide is proved as encoding human factor WW1 by written argument or certified experiment results, the above mentioned reason for rejection may be overcome. But other reasons for rejection (inventive step) will be examined.

Case 5 Full-length cDNA

Claim 1
A polynucleotide consisting of the nucleotide sequence of SEQ ID NO:9.

Description of the invention
The claimed polynucleotide is 2400bp cDNA obtained from human liver cDNA library. It encodes a polypeptide of 800 amino acids of SEQ ID NO:10. As a result of similarity search using a known DNA and amino acid database, the claimed polynucleotide showed 20 to 30% homology to the polynucleotide encoding factor ZZ1 of rat, factor ZZ2 of pig and an antagonist of factor ZZ1 receptor of monkey. And the amino acid sequence of SEQ ID NO:10 showed 20 to 30% homology to factor ZZ1 of rat, factor ZZ2 of pig and an antagonist of factor ZZ1 receptor.

Therefore, this polynucleotide encodes a human protein related to factor ZZ and may be used to diagnose patients with disease related to factor ZZ.

Result of the prior-art search
There is no known sequence with over 40% similarity to the nucleotide sequence of SEQ ID NO:9 or the amino acid sequence of SEQ ID NO:10.

Reason for rejection
As factor ZZ1, factor ZZ2, and antagonist of factor ZZ1 receptor have a different specific function to each other, mere description that the claimed polynucleotide encodes protein relating to factor ZZ does not indicate any specific function of the claimed polynucleotide. And the specific function of the corresponding protein cannot be assumed considering the state of the art as of the filing.

Therefore we consider there is no disclosure concerning the use of this polypeptide in an industrial applicable way, thus the description of the invention is deemed as insufficient for enabling a person skilled in the art to carry out the invention.

(Attention)
Even if the claimed polynucleotide is proved as encoding human protein ZZ1 by written argument or certified experiment results, the reason for rejection above may not be overcome.

3. Inventive Step : No

Case 6 Full-length cDNA

Claim 1
A polynucleotide consisting of the nucleotide sequence of SEQ ID NO:11.

Description of the invention
The claimed polynucleotide is 2700bp cDNA obtained from human liver cDNA library. It encodes a polypeptide of 900 amino acids of SEQ ID NO:12. As a result of similarity search, the amino acid sequence of SEQ ID NO:12 showed 85% homology to rat factor XX1(written in document A) and the polynucleotide sequence of SEQ ID NO:11 showed 80% homology to the polynucleotide encoding rat factor XX1(written in document A).

Therefore, this polynucleotide was assumed to encode human factor XX1 and to be useful.

Result of the prior-art search

There was no other sequence detected with over 80% similarity to that nucleotide sequence or polypeptide sequence except for rat polynucleotide encoding rat factor XX1 or the amino acid sequence of rat factor XX1. It is a well-known fact that mammalians including human have factor XX1.

Reason for rejection
It is a well-known object to prepare human DNAs encoding proteins. It is also common general knowledge to isolate the human DNA encoding a certain protein by using a partial nucleotide sequence of a mammal other than human encoding the same protein as a primer probe. Since polynucleotide encoding proteins with the same biological activities are in general highly homologous between mammalian species.

Therefore, it is obvious that the DNA encoding human factor XX1 can be isolated from human cDNA library using the partial polynucleotide encoding rat factor XX1 written in document A as a primer. And any advantageous effect cannot be acknowledged from document A or common general knowledge, hence this invention cannot be regarded as involving an inventive step.

(Attention)
The reasons for rejection above shall be determined to overcome if the applicant show specific difficulty to obtain the claimed polynucleotide with the state of the art as of the filing.

4. Enablement Requirement : No, Inventive Step : No

Case 7 DNA fragment

Claim 1
A polynucleotide consisting of the nucleotide sequence of SEQ ID NO:13.

Description of the invention
A cDNA library was constructed from human liver using oligo (dT) primers. The nucleotide sequence of SEQ ID NO:13 is one of the sequences (500 bp) which were analyzed using an automated DNA sequencer. The polynucleotide consisting of the nucleotide sequence of SEQ ID NO:13 is part of a structural gene, and it can be used as a probe in one of the steps to obtain the full-length DNA.

However, there is no working example indicating that the full-length DNA was actually obtained, and there is no description of the function or biological activity of the DNA and its corresponding protein.

Result of the prior-art search

There is no known sequence with over 30% similarity to the nucleotide sequence of SEQ ID NO:13 or the amino acid sequence of SEQ ID NO:14.

Reason for rejection

1. Inventive Step: No

It is a well-known object to obtain cDNAs from human cells and sequence them. It is also a well-known art to construct cDNA libraries from human organs, such as the liver, and to analyze the sequence of cDNA randomly chosen from the library with the use of an automated sequencer.

Therefore, for a person skilled in the art, it would have been easy to prepare cDNA library and to sequence cDNAs derived from the library using conventional methods. And the obtained DNA does not have an unexpected advantageous effect.

Hence, this invention cannot be regarded as involving an inventive step.

2. Enablement Requirement: No

An invention of a product should be described in a way enabling for a person skilled in the art to make and to use the product in an industrially applicable way (except where the product could be made and used by a person skilled in the art without such explicit description by taking into account the overall descriptions of the specification, drawings and common general knowledge as of the filing.) There is a description that the claimed DNA can be used as a probe in one of the steps to obtain a full-length DNA. However, there is no description on function or biological activity of the protein encoded by the corresponding full-length DNA. Moreover, function or biological activity of the full-length DNA cannot be assumed with common general knowledge as of the filing. The use of a DNA fragment in obtaining the full-length DNA, whose corresponding protein's function and biological activity are unknown, is not considered to be an industrially applicable use. We consider there is no disclosure concerning the use of the DNA fragment in an industrially applicable way, thus the description of the invention is deemed insufficient for enabling a person skilled in the art to carry out the invention.

(Attention)

The reasons for rejection 2 above normally shall not be overcome.

Case 8 SNPs

Claim 1

A polynucleotide of between 20 and 100 bases including position 100 (polymorphic site) of the nucleotide sequence of SEQ ID NO:14 or SEQ ID NO:15.

Description of the invention

The polynucleotide of the locus of the human genome DNAs derived from 10 persons were compared to each other. Six of 10 polynucleotide were SEQ ID NO:14 and four of 10 were SEQ ID NO:15. The nucleotide at position 100 of SEQ ID NO:14 is g. On the other hand, that of SEQ ID NO:15 is c. These two nucleotide sequences are the same except for the nucleotide at position 100. The claimed polynucleotide can be used as a forensic marker.

Result of the prior-art search
The nucleotide sequence of SEQ ID NO:14 and NO:15 are unknown. The claimed polyuncleotide is also unknown.

Reason for rejection
1. Inventive step: No
It is a well-known object to detect polymorphic site in human genome DNA. It is a well-known art to analyze and compare the sequences of genome DNAs of many persons, to detect a polymorphic site.

Therefore, for a person skilled in the art, it would have been easy to analyze and compare the sequences of a certain part of genome DNAs of several persons and to detect the polymorphic site.

And any unexpected advantageous effect cannot be acknowledged, hence this invention cannot be regarded as involving an inventive step.

2. Enablement requirement: No

An invention of a product should be described in a way enabling for a person skilled in the art to make and to use the product in an industrially applicable way. (except where the product could be made and used by a person skilled in the art without such explicit description by taking into account the overall descriptions of the specification, drawings and common general knowledge as of the filing.) Though, there is a description that the claimed nucleotide can be used as a forensic marker, only one SNP itself is not usually utilized as a forensic marker. Therefore, the mere description that the polynucleotide can be used as a forensic marker does not indicate any industrial applicable use of the claimed polynucleotide.

Attention
The reasons for rejection 2 above normally shall not be overcome.

5. Enablement Requirement : Yes, Inventive Step : Yes

Case 9 DNA fragment

Claim 1
A polynucleotide consisting of the nucleotide sequence of SEQ ID NO:16.

Description of the invention
The polynucleotide is one of the 500bp cDNAs which were found in a cDNA library derived from the hepatocyte of patients with disease Y, but not found in those of normal persons. It was confirmed by northern hybridization that the corresponding mRNAs were expressed only in the patients' hepatocyte. Therefore, the polynucleotide can be used to diagnose disease Y.

Result of the prior-art search
There is no known DNA and polypeptide which are unique in the patients with disease Y. There is no known sequence with over 30% similarity to the nucleotide sequence of SEQ ID NO:16.

Reason for rejection
No reason for rejection

Case 10 Full-length cDNA

Claim 1
A polynucleotide consisting of the nucleotide sequence of SEQ ID NO:17.

Description of the invention
The claimed polynucleotide is 2700bp cDNA obtained from human liver cDNA library. It encodes a polypeptide of 900 amino acids of SEQ ID NO:18. This polypeptide was expressed and it showed the activity of human factor YY1.

Result of the prior-art search
There is no known sequence with over 80% similarity to the nucleotide sequence of SEQ ID NO:17 or the amino acid sequence of SEQ ID NO:18. And no prior art was found about the human factor YY1.

Reason for rejection
No reason for rejection

Attention
The specific function of the factor YY1 is known.

Case 11 SNP

Claim 1
A polynucleotide of between 20 and 100 bases including position 50(g) (polymorphic site) of the nucleotide sequence of SEQ ID NO:19.

Description of the invention
The polynucleotide of SEQ ID NO:20 is known. The nucleotide at position 50 of SEQ ID NO:19(500 length DNA) is g. On the other hand, that of SEQ ID NO:20 is c. These two nucleotides are the same except for the nucleotide at position 50. The nucleotide at position 50 of the polynucleotide of SEQ ID NO:19 is proved to be polymorphic site. A polynucleotide of between 20 and 100 bases including position 50 (g) of the nucleotide sequence of SEQ ID NO:19 is experimentally proved to be used to diagnose disease Z.

Result of the prior-art search
The polynucleotide sequence of SEQ ID NO:19 was not known. The claimed polynucleotide was neither known. Relationship between the polymorphic site at position 50 and disease Z was not known. Though the polynucleotide of SEQ ID NO:20 is known to be a part of structural gene, the relationship between the protein encoded by the structural gene and disease Z was not known.

Reason for rejection
No reason for rejection

Biotech-related Patent System in Korea

1. LEGISLATION SYSTEM

A. Patent Law

With the exception of plant invention, there is no any special provision just for biotech-related inventions in Patent Law.

> *Requirement of Disclosure and Claims, Industrial Applicability, Novelty, Inventive step, Unity of Invention, etc*

The patent of plant invention can be granted if it satisfies the provision of Patent Law Article 31 (*"Plant Invention").*

> *A variety of plant which reproduces itself asexually may obtain a plant patent.*

In addition, Seed Industry Law was enforced on December, 1997 to protect plant varieties by *sui generis* system. (According to TRIPs Article 27.3(b))

An ethical restriction on the patentability of biotech-related inventions is judged under the provision of Patent Law Article 32 (*"Unpatentable Inventions").*

> *Inventions liable to contravene public order or morality or to injury public health shall not be patentable*.

B. "Patent Examination Guideline for Biotechnological Inventions"

To examine the patentability of biotechnological inventions more efficiently, **Patent Examination Guideline for Biotechnological Inventions** was established in 1998.

> *4 Sectors: Genetic Engineering Inventions, Microorganism Inventions, Plant Inventions and Animal Inventions*

This Guideline is amended to reinforce specific standards for the product of Human Genome Project, such as EST or SNP. The amended one is enforced on January, 2001.

2. EFFICIENT EXAMINATION SYSTEM AT KIPO

Genetic Engineering Examination Division at KIPO is in charge of examination of Biotech-related invention. Besides, Pharmaceutical Examination Division and Agricultural Forestry & Fishery Examination Division also take part in examining biotech-related inventions.

Biotechnology Patent Sequence Search System (BIOPASS) has been established in '99. for nucleotide or amino acids sequence search. It is open to the public from Jan. 2000.

3. DEPOSITORY SYSTEM FOR MICROORGANISM

A. Backgrounds

In invention where a starting material or final product includes biological materials such as a microorganism, as a creature whose structure is complicated becomes an essential constitutional factor of the invention, frequently, the claimed invention may not be easily reproduced only based on the disclosure of the specification.

Therefore, if a starting material may not easily be obtained, the starting material should be deposited, and in an invention where a final product cannot be readily produced by only the disclosure of the specification, the final products should be deposited, thereby providing that a person having ordinary skill in the art can easily practice the invention.

B. Deposit of microorganism and disclosure by specification

Any person desiring to file a patent application in connection with an invention related to a microorganism shall be deposit the microorganism with a deposit agency or an international depositary authority approved by the director of KIPO and state the deposit number in the specification at the time of filing.

Furthermore, when a new deposit number is assigned to the prior-deposited microorganism by redepositing after filing, delivery to other international depositary authority, or a change from domestic deposit to that under the Budapest Convention, the applicant or patentee should immediately notify the Director of KIPO of the same and new deposit number.

C. Depositary Authorities in Korea

There are 2 Domestic Depositary Authorities.
- Korean Research Institute of Bioscience & Biotechnology
- Korean Culture Center of Microorganism

There are 3 International Depositary Authorities.
- Korean Research Institute of Bioscience & Biotechnology
- Korean Culture Center of Microorganism
- Korean Cell Line Research Foundation

Brief Outline of *Patent Examination Guideline for Biotechnological Inventions in Korea*

1. Genetic Engineering Inventions

A. Description Method for Specification

A-1. Patent claims

(1) Gene

- A gene is, in principle, described by specifying a base sequence.
- A structural gene can be described by specifying an amino acid sequence of proteins which a base sequence encodes.
- When the expression, "being deleted, replaced or added", is used along with a base sequence of a gene, the position thereof should be clarified.

(2) Vector

- A vector should be described in combination of a DNA base sequence, cleavage map of DNA, molecular weight, number of base pairs, origin, production method, function, characteristics, etc.

(3) Recombinant Vector

- A recombinant vector should be described by specifying the inserted gene and a vector

(4) Transformants

- Transformants should be described specifying a host designed by its species name or generic name according to nomenclature for microorganism, plants or animals and the introduced recombinant vector (or a gene).

(5) Proteins and recombinant protein

- Proteins and recombinant proteins should be described by specifying amino acid sequence or base sequence of structural gene encoding said amino acid sequence. However, when an expression such as "deletion", "replacement" or "addition" is used, the position should be clearly disclosed.

- When a protein can not be described by specifying as above, the protein can be described by specifying in combination of function, physiochemical property, origin, source, or production process of the protein.

A-2. Detailed Description of Invention

- The detailed description of the invention should be the purpose, construction, and effect of the invention in such a manner that it may easily be carried out by a person having ordinary skill in the relevant art.

A-3. Sequence Listing

- When a base sequence of nucleic acid consisting of ten or more nucleotides or an amino acid sequence of protein consisting four or more L-amino acids is described in the detailed description of the invention, the sequence should be prepared in accordance with the preparation guidelines for the specification, and be attached at the end of the detailed description of the invention.

- When a base sequence or amino acid sequence is to be described in the claim, the sequence described in the sequence listing prepared according to above Para. can be cited.

B. Inventions Corresponding to Unpatentable Reasons

- Genetic engineering inventions are deemed to be unpatentable under the provision of Patent Law Article 32, when, they are liable to contravene public order or morality or damage public health, as set forth below.
    - Invention liable to destroy the ecosystem
    - Invention liable to cause environmental contamination
    - Invention liable to hurt human beings
    - Invention liable to cause a result denigrating the dignity of human being

C. Patent Requirements

C-1. Establishment of Invention

(1) The following cases are not acknowledged to be complete as an invention according to the provision of Patent Act Article 29.1

- When corresponding to a mere discovery.
- Inventions directed to a gene, vector, recombinant vector, transformant, fused cell, monoclonal antibody, protein, recombinant protein, where specific production methods thereof are not described in detail in the specification.

(2) However, an invention is deemed to be complete when the gene or protein is artificially isolated and identified from a living thing, and its function is clarified.

C-2. Industrial Applicability

(1) Utility should be described.

(2) A method of treating or diagnosing a human being is not acknowledged as an [industrial applicable] invention according to the provision of text under the Patent Law Article 29.1.

C-3. Novelty

(1) Genes, vector, recombinant vector, protein, recombinant protein

- In principle, novelty is determined with priority given to the structure.
- When a gene, vector, recombinant vector, protein, recombinant protein
- is publicly known as an isolated and purified form and is differentiated as a separate material in comparison with known materials by being specified with different specific means, the claimed matter is deemed novel.

- Where a recombinant protein specified by a recombinant process exhibits a difference in its sugar chain, etc. from a publicly known protein due to the use of a different host, even though the recombinant protein cannot be differentiated in the amino acid sequence from the above publicly known protein, the claimed recombinant protein is deemed novel.

(2) Fused cells
- Novelty of a fused cell is determined based on the mother cell used or the monoclonal antibody produced.

(3) Monoclonal antibody
- Novelty of a monoclonal antibody is determined based on the antigen and its epitope.

2. Microorganism Inventions

A. Description Method for Specification

- Microorganism means virus, bacteria, protozoa, yeasts, fungi, mushrooms, unicellular algae, actinomyces, etc. and include non-specialized cells of animals and plants and tissue culture as well.

A-1. Patent claims

(1) Inventions of a microorganism
- A microorganism should be described by specifying its scientific name, and a deposit number or mycological property by which the corresponding microorganism is characterized may be added for further specification.
- Non-specialized cells of animals and plants should be described by specifying with their scientific name based on nomenclature for animals or plants which they were derived from, and the name of deposit agency and deposit number may be added for further specification.

(2) Inventions using microorganisms
- When using a novel strain, mutant strain or prior art strain, it should be described by its strain name.
- When using a novel species, mutant species or species, it should be described by its species name.

A-2. Detailed Description of Invention

(1) Repetitious reproducibility should be supported.
- When it is difficult to describe a process for producing the microorganism, they should be deposited with the depositary authority appointed by Patent Law Enforcement Ordinance Article 2.

(2) When a novel microorganism is described, its species name based nomenclature for microorganism, or strain name to which its species name was added should be indicated along with mycological properties.

(3) In inventions regarding a microorganism or use of microorganism, a manufacturing process thereof such as isolation, purification method, screening method, mutant producing method,

gene recombination process should be described in detail in order for a person having ordinary skill in the art to easily produce the microorganism.

B. Patent Requirements

B-1. Establishment of Invention

The following cases are not recognized to be complete as an invention according to the provision of Patent Law Article 29.1

(1) When corresponding to a mere discovery.
- However, an invention is deemed to be complete, when related to a microorganism which was artificially isolated from nature and identified.

(2) When the microorganism used is unclear, since the microorganism used is novel or its taxonomical properties are insufficiently described in the specification.

(3) When the material produced by using microorganism is novel or data by which the material may be identified are not sufficiently described.

B-2. Industrial Applicability & Novelty

- Industrial applicability & Novelty are determined according to the provision under the Patent Law Article 29.1.

3. Plant Inventions

A. Description Method for Specification

A-1. Patent claims

The following must be described to avoid the violation of Article 42.4 of the Patent Law.

(1) For Inventions to a variety plant or part of a variety plant.
- The title of the plant, Property of the plant or characteristic genes and Asexual production process

(2) For Inventions of breeding process for variety plants
- Order of steps of the breeding procedure, Specific condition such as the environment for the breeding process, and Characteristic which are the standard for selection

(3) For Inventions of asexual reproduction methods for variety plants
- Characteristic properties of the plants or a gene, and Asexual reproduction method

A-2. Detailed Description of Invention

(1) Repetitious reproducibility should be supported.

(2) Technical tasks solved by an invention should be described as follows.

- Characteristics of prior art plants to be improved
- Specific method in order to improve specific characteristic
- Specific asexual reproduction method to propagate variety plants

(3) Providing means in order to solve technical tasks, that is, the title of variety plant (scientific name by botanical nomenclature), property, breeding, asexual reproduction method, culture condition, use, etc. should be specifically disclosed.

B. Patent Requirements

B-1. Establishment of Invention

- When corresponding to a mere discovery in an invention of a variety plant, such a invention is not deemed to be complete as an invention under Patent Law Article 29.1.

B-2. Industrial Applicability

- In an invention directed to an asexually variety plant, if utility is not described nor can be inferred therefrom, the invention is not deemed as an industrially applicable invention of under the Article 29.1

B-3. Invention Step

- In determining the inventive step of an invention regarding a bred variety plant, it is determined with priority given to characteristics.
    - Esculent plants : characteristics such as content of nutrient
    - Medicinal plants : characteristics such as content of effective ingredient, quantity
    - Ornamental plants : characteristics such as color, shape, quantity

4. Animal Inventions

A. Description Method for Specification

A-1. Patent claims

(1) Animals should be described by specifying the title of an animal, a gene or property which becomes the characteristic of the animal and creating process for the animal, and may be specified by adding deposit (such as embryo) authority and deposit number.

(2) Inventions directed to a process for creating an animal should disclose the procedure for creating the animal following the order of steps, property which becomes the standard for selection, and if necessary, production condition such as the environment.

A-2. Detailed Description of Invention

(1) Repetitious reproducibility should be supported.

(2) Scientific name based on zoological nomenclature and the standard Korean name should be described.

(3) Properties by which the created animal can be characterized should be described.

(4) Where required, specific breeding conditions should be described.

B. Patent Requirements

B-1. Industrial Applicability

- In an invention directed to an asexually variety plant, if utility is not described nor can be inferred therefrom, the invention is not deemed as an industrially applicable invention of under the Article 29.1.

B-2. Invention Step

- Inventive step of inventions directed to an animal is determined based on the characteristics in comparison with those of prior art animals and the effect in terms of the use thereof.
- Inventive step for a process is determined based on difficulty in selecting means, condition corresponding to respective procedure of the manufacturing process of the novel animal and inventive step of the animal finally made.

Patentability Criteria of Biotechnological Inventions

Intellectual Property Office of New Zealand (IPONZ)

Biotechnological inventions are examined under the New Zealand Patents Act 1953. This legislation is presently being reviewed, and this review will take into account the findings of the recent enquiry by the Royal Commission on Genetic Modification (not yet released). This may lead to some restriction being placed on the patentability of inventions involving genetic modification. Also of interest is that the proposed patents bill, if passed, will allow New Zealand to accede to the Budapest Treaty.

At present, claims involving biotechnology may be accepted by IPONZ so long as the established requirements for a patent are satisfied, such as the conditions of a manner of new manufacture are met (including the creation of an artificial state of affairs for which there is a commercial application), novelty, and the technology is fairly and sufficiently described in the specification. It is essential that a clear description of the technology be provided and it is sufficient to distinguish the present technology from all known technology and the best method of performing the invention known to the applicant is disclosed.

Claims involving DNA sequences are viewed by the office in the same light as chemical compounds, in that each variable within the sequences is disclosed; i.e. the scope of the claim is well defined.

Biotechnology applications differ in the blend of objections that are made. Because biotechnological inventions deal more often with naturally-occurring products than other kinds of applications, there are more objections asking the applicant to exclude the product as found in nature by specifying that the product is in isolated or purified form. Biological inventions are often medically applicable so there are more objections that the applications include the medical treatment of humans.

Biotechnology is a new and developing science and does not fit neatly with law here, and in many countries, and with old case law. This means that practice is, and has to be, in a process of development to ensure that the law is applied and that technological developments are protected where appropriate or possible.

Biotechnology is controversial. The implications of the Treaty of Waitangi apply more to these applications. There is a claim before the Waitangi tribunal relating to native flora and fauna. Biotechnology is generally controversial too, from aspects of morality and safety of the research and products developed.

It should also be noted that NZ patent law and practice complies fully with the TRIPS agreement, especially article 27.3 relating to the patentable subject matter. Article 27.3 (b) of the TRIPS Agreement in 1999 enables members of the Agreement to exclude from patentability:

"plants and animals other than micro-organisms, and essentially biological processes for the production of plants or animals, other than non-biological and microbiological processes".

Claims involving method of treatment to humans are currently objected to under Section 17 of the New Zealand Patents Act 1953.

> *S17. Refusal of application in certain cases-(1)if it appears to the Commissioner in the case of any application for a patent that the use of the invention in respect of which the application is made would be contrary to morality, the Commissioner may refuse the application.*
> *(2) An appeal to the court shall lie from any decision of the Commissioner under this section.*

In *The Commissioner Of Patents* v. *The Wellcome Foundation Ltd*, Court of Appeal [1983] FSR 593, McMullin J. stated:

> *"traditionally patents have not been granted for a method of treatment of disease or illness in human beings" (p603);*

and on change of practice in this area McMullin J. stated:

> *"any major thrust should be left to Parliament" (p609).*

In a recent decision on a case including Swiss-type claims, *Pharmaceutical Management Agency Limited* v *Commissioner of Patents and Others*, it was deemed that methods of treatment involving humans are inventive, therefore allowable under Section 2 as a method of new manufacture. This does not give such claims patentability under Section 17, however.

Parliament must make any major change in the law on the granting of patents for methods of treating disease or illness in humans to be patentable. However there is scope for minor changes.

The current practice for IPONZ to continue to refuse claims involving method(s) of treating human under Section 17 pending the outcome of a decision from the courts. There is presently a case on appeal from a decision of the Commissioner waiting to be heard by the court in this regard.

1 May 2001

Patenting and Biotechnology

In Singapore[5]

LAW

(a) The main statute on patents in Singapore is the Patents Act (Cap. 221), Revised Edition 1995 and as amended by the Patents (Amendment) Act 1995 (Act 40 of 1995 with effect from 1 January 1996). Copies of the legislation can be purchased from myepb Bookstore Legal Publications at No. 3 Temasek Boulevard, B1-025 Suntec City Mall Singapore 038983 (Tel: 333-9703). The web-site address is: (http://www.myepb.com/script/legalpub.asp).

(b) In Singapore, section 13 of our Patents Act states a patentable invention is one that is new, has inventive step and is capable of industrial application. The various concepts of "new", "inventive step" and "industrial application", present in this section (and its related provisions in sections 14 to 16), have been developed and discussed in case law before the UK and European courts.

(c) Our Patents Act also contains provisions (sections 14 to 16) that explain the requirements of novelty (novelty destroying matter is anything that had been made anywhere in the world, through any means, before the priority date of the invention), inventive step (the invention must not be obvious to a person skilled in the art), and capable of industrial application (method of treatment of the human or animal body by surgery, or therapy or of diagnosis practiced on the human or animal body shall not be capable of industrial application – section 16(2)).

(d) We would add that in the case of an invention consisting of a substance or composition for use in a method of treatment of the human or animal body by surgery or therapy or of diagnosis practiced on the human or animal body, section 14(7) provides that the fact that the substance or composition is not new shall not prevent the invention from being taken to be new if the use of the substance or composition in any such method is not known.

(e) Over and above the requirements of novelty, inventive step and industrial application, an invention is not patentable if the publication or exploitation of which would generally be expected to encourage offensive, immoral or antisocial behavior (section 13(3)).

(f) As the patents system serves as a *quid pro quo* for the disclosure of inventions, thereby benefiting mankind, there are stringent requirements in place to ensure that this objective is achieved. In most jurisdictions, applicants are required to disclose their inventions in the patent applications in a clear and complete manner so as to enable a person skilled in the art to perform the invention. In Singapore, this requirement is found in section 25 of the Patents Act. Failure to comply with this requirement can serve as a ground for revocation of a granted patent (Section 80 of the Patents Act).

[5] Information as of 11 April 2001, provided by Assistant Registrar of Patents, Singapore

(g) Our Patents Act does not have a positive definition of what an "invention" is. Our Patents Act also does not have a list of statutory exclusions (unlike the United Kingdom and the European Patent Convention where certain things like discovery, scientific theory, mathematical method and aesthetic creations are expressly excluded from being considered as "inventions"). The question of whether a particular "subject matter" is an invention is therefore left to judicial interpretation on a case-by-case basis, as is the case with other requirements on patentability (e.g. new, inventive step and industrial application).

JUDICIAL INTERPRETATION

Two Singapore Court of Appeal decisions on patents were released last year i.e. Merck v. Pharmaforte (this case involved a pharmaceutical drug) & Institut Pasteur v. Genelabs (the invention in question relates to a HIV-2 virus) and it would be noted that the case law developed in UK and Europe were discussed and relied upon. It is therefore likely that our courts would continue to find the UK and European case law on similar provisions, to be persuasive.

EXAMINATION GUIDELINES

In Singapore, section 29 of the Patents Act provides applicants with several options for search and examination. In brief, they can rely on foreign corresponding prescribed search and examination equivalents in lieu of requesting the Registry to conduct a search and examination for them, or file a search and examination request with us.

On search and examination, our Examiners i.e. from the Australian and Austrian Patent Offices, are regularly kept informed of any local statutory or judicial changes on patents. Preliminary objections to patentability could be raised in the written opinions, providing applicants with an opportunity to respond.

In the event where applicants rely on their foreign corresponding prescribed search and examination equivalents in lieu of filing search and examination requests with us, they should take into consideration our Patents Law and any corresponding judicial decisions. We would add that our patents system promotes self-assessment, and applicants are therefore encouraged to make necessary amendments (within the scope of section 84 of the Patents Act) to their specification if any, before they seek for the Grant Certificate.

United States
Utility Examination Guidelines [6]

AGENCY: United States Patent and Trademark Office, Commerce

ACTION: Notice

SUMMARY: The United States Patent and Trademark Office (USPTO) is publishing a revised version of guidelines to be used by Office personnel in their review of patent applications for compliance with the 'utility' requirement of 35 U.S.C. 101

This revision supersedes the Revised Interim Utility Examination Guidelines that were published at 64 FR 71440, Dec. 21, 1999; 1231 O.G. 136 (2000); and correction at 65 FR 3425, Jan. 21, 2000; 1231 O.G. 67 (2000)

DATES: The Guidelines are effective as of January 5, 2001

FOR FURTHER INFORMATION CONTACT: Mark Nagumo by telephone at (703) 305–8666, by facsimile at (703) 305– 9373, by electronic mail at 'mark.nagumo@uspto.gov,' or by mail marked to his attention addressed to the Office of the Solicitor, Box 8, Washington, DC 20231; or Linda Therkorn by telephone at (703) 305– 9323, by facsimile at (703) 305–8825, by electronic mail at 'linda.therkorn@uspto.gov,' or by mail marked to her attention addressed to Box Comments, Commissioner for Patents, Washington, DC 20231

SUPPLEMENTARY INFORMATION: As of the publication date of this notice, these Guidelines will be used by USPTO personnel in their review of patent applications for compliance with the 'utility' requirement of 35 U.S.C. 101

Because these Guidelines only govern internal practices, they are exempt from notice and comment rulemaking under 5 U.S.C. 553(b)(A)

I. Discussion of Public Comments

The Revised Interim Utility Examination Guidelines published at 64 FR 71440, Dec. 21, 1999; 1231 O.G. 136, Feb. 29, 2000, with a correction at 65 FR 3425, Jan. 21, 2000; 1231 O.G. 67, Feb 15, 2000, requested comments from the public. Comments were received from 35 individuals and 17 organizations

The written comments have been carefully considered

Overview of Comments

The majority of comments generally approved of the guidelines and several expressly stated support for the three utility criteria (specific, substantial, and credible) set forth in the Guidelines. A few comments addressed particular concerns with respect to the coordinate examiner training materials that are available for public inspection at the USPTO website, *www.uspto.gov*. The comments on the training materials will be taken under advisement in the revision of the training materials

Consequently, those comments are not specifically addressed below because they do not impact the

[6] **1092 Federal Register** / Vol. 66, No. 4 / Friday, January 5, 2001 / Notices
DEPARTMENT OF COMMERCE United States Patent and Trademark Office [Docket No. 991027289–0263–02] RIN 0651–AB09

content of the Guidelines. Comments received in response to the request for comments on the 'Revised Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶1 'Written Description' Requirement,' 64 FR 71427, Dec. 21, 1999; 1231 O.G. 123, Feb. 29, 2000, which raised issues pertinent to the utility requirement are also addressed below

Responses to Specific Comments

(1) ***Comment***: Several comments state that while inventions are patentable, discoveries are not patentable. According to the comments, genes are discoveries rather than inventions. These comments urge the USPTO not to issue patents for genes on the ground that genes are not inventions.

Response: The suggestion is not adopted. An inventor can patent a discovery when the patent application satisfies the statutory requirements. The U.S. Constitution uses the word 'discoveries' where it authorizes Congress to promote progress made by inventors. The pertinent part of the Constitution is Article 1, section 8, clause 8, which reads: 'The Congress shall have power * * * To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries.'

When Congress enacted the patent statutes, it specifically authorized issuing a patent to a person who 'invents or discovers' a new and useful composition of matter, among other things. The pertinent statute is 35 U.S.C. 101, which reads: 'Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.' Thus, an inventor's discovery of a gene can be the basis for a patent on the genetic composition isolated from its natural state and processed through purifying steps that separate the gene from other molecules naturally associated with it.

If a patent application discloses only nucleic acid molecular structure for a newly discovered gene, and no utility for the claimed isolated gene, the claimed invention is not patentable. But when the inventor also discloses how to use the purified gene isolated from its natural state, the application satisfies the 'utility' requirement. That is, where the application discloses a specific, substantial, and credible utility for the claimed isolated and purified gene, the isolated and purified gene composition may be patentable.

(2) ***Comment***: Several comments state that a gene is not a new composition of matter because it exists in nature, and/ or that an inventor who isolates a gene does not actually invent or discover a patentable composition because the gene exists in nature. These comments urge the USPTO not to issue patents for genes on the ground that genes are products of nature. Others state that naturally occurring DNAs are part of our heritage and are not inventions. Another comment expressed concern that a person whose body includes a patented gene could be guilty of patent infringement.

Response: The comments are not adopted. A patent claim directed to an isolated and purified DNA molecule could cover, *e.g.*, a gene excised from a natural chromosome or a synthesized DNA molecule. An isolated and purified DNA molecule that has the same sequence as a naturally occurring gene is eligible for a patent because (1) an excised gene is eligible for a patent as a composition of matter or as an article of manufacture because that DNA molecule does not occur in that isolated form in nature, or (2) synthetic DNA preparations are eligible for patents because their purified state is different from the naturally occurring compound.

Patenting compositions or compounds isolated from nature follows well-established principles, and is not a new practice. For example, Louis Pasteur received U.S. Patent 141,072 in 1873, claiming '[y]east, free from organic germs of disease, as an article of manufacture.' Another example is an early patent for adrenaline. In a decision finding the patent valid, the court explained that compounds isolated from nature are patentable: 'even if it were merely an extracted product without change, there is no rule that such products are not patentable. Takamine was the first to make it [adrenaline] available for any use by removing it from the other gland-tissue in which it was found, and, while it is of course possible logically to c all this a purification of the principle, it became for every practical purpose a new thing commercially and therapeutically. That was a good ground for a patent.' *Parke- Davis & Co.* v. *H. K. Mulford Co.,* 189 F. 95, 103 (S.D.N.Y. 1911) (J. Learned Hand).

In a more recent case dealing with the prostaglandins PGE2 and PGE3, extracted from human or animal prostate glands, a patent examiner had rejected the claims, reasoning that 'inasmuch as the 'claimed compounds are naturally occurring' * * * they therefore 'are not 'new' within the connotation of the patent statute.' ' *In re Bergstrom*, 427 F.2d 1394, 1397, 166 USPQ 256, 259 (CCPA 1970). The Court reversed the Patent Office and explained the error: 'what appellants claim—pure PGE2 and PGE3—is not 'naturally occurring.' Those compounds, as far as the record establishes, do not exist in nature in pure form, and appellants have neither merely discovered, nor claimed sufficiently broadly to encompass, what has previously existed in fact in nature's storehouse, albeit unknown, or what has previously been known to exist.' *Id.* at 1401, 166 USPQ at 261–62. Like other chemical compounds, DNA molecules are eligible for patents when isolated from their natural state and purified or when synthesized in a laboratory from chemical starting materials.

A patent on a gene covers the isolated and purified gene but does not cover the gene as it occurs in nature. Thus, the concern that a person whose body 'includes' a patented gene could infringe the patent is misfounded. The body does not contain the patented, isolated and purified gene because genes in the body are not in the patented, isolated and purified form

When the patent issued for purified adrenaline about one hundred years ago, people did not infringe the patent merely because their bodies naturally included unpurified adrenaline

(3) ***Comment***: Several comments suggested that the USPTO should seek guidance from Congress as to whether naturally occurring genetic sequences are patentable subject matter.

Response: The suggestion is not adopted. Congress adopted the current statute defining patentable subject matter (35 U.S.C. 101) in 1952. The legislative history indicates that Congress intended 'anything under the sun that is made by man' to be eligible for patenting. S. Rep. No. 1979, 82d Cong., 2d Sess., 5 (1952); H.R. Rep No. 1923, 82d Cong., 2d Sess., 6 (1952)

The Supreme Court interprets the statute to cover a 'nonnaturally occurring manufacture or composition of matter—a product of human ingenuity.' *Diamond* v. *Chakrabarty*, 447 U.S. 303, 309, 206 USPQ 193, 197 (1980). Thus, the intent of Congress with regard to patent eligibility for chemical compounds has already been determined: DNA compounds having naturally occurring sequences are eligible for patenting when isolated from their natural state and purified, and when the application meets the statutory criteria for patentability. The genetic sequence data represented by strings of the letters A, T, C and G alone is raw, fundamental sequence data, i.e., nonfunctional descriptive information.

While descriptive sequence information alone is not patentable subject matter, a new and useful purified and isolated DNA compound described by the sequence is eligible for patenting, subject to satisfying the other criteria for patentability.

(4) ***Comment***: Several comments state that patents should not issue for genes because the sequence of the human genome is at the core of what it means to be human and no person should be able to own/control something so basic. Other comments stated that patents should be for marketable inventions and not for discoveries in nature.

Response: The comments are not adopted. Patents do not confer ownership of genes, genetic information, or sequences. The patent system promotes progress by securing a complete disclosure of an invention to the public, in exchange for the inventor's legal right to exclude other people from making, using, offering for sale, selling, or importing the composition for a limited time. That is, a patent owner can stop infringing activity by others for a limited time.

Discoveries from nature have led to marketable inventions in the past, but assessing the marketability of an invention is not pertinent to determining if an invention has a specific, substantial, and credible use. '[D]evelopment of a product to the extent that it is presently commercially salable in the marketplace is not required to establish 'usefulness' within the meaning of § 101.' *In re Langer*, 503 F.2d 1380, 1393, 183

USPQ 288, 298 (CCPA 1974). Inventors are entitled to patents when they have met the statutory requirements for novelty, nonobviousness and usefulness, and their patent disclosure adequately describes the invention and clearly teaches others how to make and use the invention. The utility requirement, as explained by the courts, only requires that the inventor disclose a practical or real world benefit available from the invention, i.e., a specific, substantial and credible utility. As noted in a response to other comments, it is a long tradition in the United States that discoveries from nature which are transformed into new and useful products are eligible for patents.

(5) ***Comment***: Several comments state that the Guidelines mean that anyone who discovers a gene will be allowed a broad patent covering any number of possible applications even though those uses may be unattainable and unproven. Therefore, according to these comments, gene patents should not be issued.

Response: The comment is not adopted. When a patent claiming a new chemical compound issues, the patentee has the right to exclude others from making, using, offering for sale, selling, or importing the compound for a limited time. The patentee is required to disclose only one utility, that is, teach others how to use the invention in at least one way. The patentee is not required to disclose all possible uses, but promoting the subsequent discovery of other uses is one of the benefits of the patent system. When patents for genes are treated the same as for other chemicals, progress is promoted because the original inventor has the possibility to recoup research costs, because others are motivated to invent around the original patent, and because a new chemical is made available as a basis for future research. Other inventors who develop new and nonobvious methods of using the patented compound have the opportunity to patent those methods.

(6) ***Comment***: One comment suggests that the USPTO should not allow the patenting of ESTs because it is contrary to indigenous law, because the Supreme Court's *Diamond* v. *Chakrabarty* decision was a bare 5-to-4 decision, because it would violate the Thirteenth Amendment of the U.S. Constitution, because it violates the novelty requirement of the patent laws, because it will exacerbate tensions between indigenous peoples and western academic/research communities and because it will undermine indigenous peoples' own research and academic institutions. The comment urges the USPTO to institute a moratorium on patenting of life forms and natural processes.

Response: The comments are not adopted. Patents on chemical compounds such as ESTs do not implicate the Thirteenth Amendment. The USPTO must administer the patent statutes as the Supreme Court interprets them. When Congress enacted § 101, it indicated that 'anything under the sun that is made by man' is subject matter for a patent. S. Rep. No. 1979, 82d Cong., 2d Sess., 5 (1952); H.R. Rep. No 1923, 82d Cong., 2d Sess., 6 (1952). The Supreme Court has interpreted § 101 many times without overturning it. *See, e.g., Diamond* v. *Diehr,* 450 U.S. 175, 209 USPQ 1 (1981) (discussing cases construing section 101). Under United States law, a patent applicant is entitled to a patent when an invention meets the patentability criteria of title 35. Thus, ESTs which meet the criteria for utility, novelty, and nonobviousness are eligible for patenting when the application teaches those of skill in the art how to make and use the invention.

(7) ***Comment***: Several comments state that patents should not issue for genes because patents on genes are delaying medical research and thus there is no societal benefit associated with gene patents. Others state that granting patents on genes at any stage of research deprives others of incentives and the ability to continue exploratory research and development. Some comment that patentees will deny access to genes and our property (our genes) will be owned by others.

Response: The comments are not adopted. The incentive to make discoveries and inventions is generally spurred, not inhibited, by patents. The disclosure of genetic inventions provides new opportunities for further development. The patent statutes provide that a patent must be granted when at least one specific, substantial and credible utility has been disclosed, and the application satisfies the other statutory requirements. As long as one specific, substantial and credible use is disclosed and the statutory requirements are met, the USPTO is not authorized to withhold the patent until another, or better, use is discovered. Other researchers may discover higher, better or more practical uses, but they are

advantaged by the starting point that the original disclosure provides. A patent grants exclusionary rights over a patented composition but does not grant ownership of the composition. Patents are not issued on compositions in the natural environment but rather on isolated and purified compositions.

(8) ***Comment****:* Several comments stated that DNA should be considered unpatentable because a DNA sequence by itself has little utility.

Response: A DNA sequence—*i.e.*, the sequence of base pairs making up a DNA molecule— is simply one of the properties of a DNA molecule. Like any descriptive property, a DNA sequence itself is not patentable. A purified DNA *molecule* isolated from its natural environment, on the other hand, is a chemical compound and is patentable if all the statutory requirements are met. An isolated and purified DNA molecule may meet the statutory utility requirement if, *e.g.*, it can be used to produce a useful protein or it hybridizes near and serves as a marker for a disease gene. Therefore, a DNA molecule is not *per se* unpatentable for lack of utility, and each application claim must be examined on its own facts

(9) ***Comment****:* One comment states that the disclosure of a DNA sequence has inherent value and that possible uses for the DNA appear endless, even if no single use has been worked out. According to the comment, the 'basic social contract of the patent deal' requires that such a discovery should be patentable, and that patenting should be 'value-blind.'

Response: The comment is not adopted. The Supreme Court did not find a similar argument persuasive in *Brenner* v. *Manson*, 383 U.S. 519 (1966). The courts interpret the statutory term 'useful' to require disclosure of at least one available practical benefit to the public. The Guidelines reflect this determination by requiring the disclosure of at least one specific, substantial, and credible utility. If no such utility is disclosed or readily apparent from an application, the Office should reject the claim. The applicant may rebut the Office position by showing that the invention does have a specific, substantial, and credible utility that would have been recognized by one of skill in the art at the time the application was filed

(10) ***Comment****:* Several comments stated that the scope of patent claims directed to DNA should be limited to applications or methods of using DNA, and should not be allowed to encompass the DNA itself.

Response: The comment is not adopted. Patentable subject matter includes both 'process[es]' and 'composition[s] of matter.' 35 U.S.C. 101. Patent law provides no basis for treating DNA differently from other chemical compounds that are compositions of matter. If a patent application claims a composition of matter comprising DNA, and the claims meet all the statutory requirements of patentability, there is no legal basis for rejecting the application

(11) ***Comment****:* Several comments stated that DNA patent claim scope should be limited to uses that are disclosed in the patent application and that allowing patent claims that encompass DNA itself would enable the inventor to assert claims to 'speculative' uses of the DNA that were not foreseen at the time the patent application was filed.

Response: The comment is not adopted. A patent on a composition gives *exclusive* rights to the composition for a limited time, even if the inventor disclosed only a single use for the composition. Thus, a patent granted on an isolated and purified DNA composition confers the right to exclude others from *any* method of using that DNA composition, for up to 20 years from the filing date. This result flows from the language of the statute itself. When the utility requirement and other requirements are satisfied by the application, a patent granted provides a patentee with the right to exclude others from, *inter alia*, 'using' the patented composition of matter. *See* 35 U.S.C.154. Where a new use is discovered for a patented DNA composition, that new use may qualify for its own process patent, notwithstanding that the DNA composition itself is patented. By statute, a patent is required to disclose one practical utility. If a well-established utility is readily apparent, the disclosure is deemed to be implicit. If an application fails to disclose one specific, substantial, and credible utility, and the examiner discerns no well-established

utility, the examiner will reject the claim under section 101. The rejection shifts the burden to the applicant to show that the examiner erred, or that a well-established utility would have been readily apparent to one of skill in the art. The applicant cannot rebut the rejection by relying on a utility that would not have been readily apparent at the time the application was filed. *See, e.g., In re Wright,* 999 F.2d 1557, 1562–63, 27 USPQ2d 1510, 1514 (Fed. Cir. 1993) ('developments occurring after the filing date of an application are of no significance regarding what one skilled in the art believed as of the filing date')

(12) ***Comment***: Several comments stated that DNA should be freely available for research. Some of these comments suggested that patents are not necessary to encourage additional discovery and sequencing of genes. Some comments suggested that patenting of DNA inhibits biomedical research by allowing a single person or company to control use of the claimed DNA. Another comment expressed concern that patenting ESTs will impede complete characterization of genes and delay or restrict exploration of genetic materials for the public good

Response: The scope of subject matter that is eligible for a patent, the requirements that must be met in order to be granted a patent, and the legal rights that are conveyed by an issued patent, are all controlled by statutes which the USPTO must administer. 'Whoever invents or discovers any new and useful * * * composition of matter * * * may obtain a patent therefor.' 35 U.S.C. 101. Congress creates the law and the Federal judiciary interprets the law. The USPTO must administer the laws as Congress has enacted them and as the Federal courts have interpreted them. Current law provides that when the statutory patentability requirements are met, there is no basis to deny patent applications claiming DNA compositions, or to limit a patent's scope in order to allow free access to the use of the invention during the patent term.

(13) ***Comment***: Several comments suggested that DNA sequences should be considered unpatentable because sequencing DNA has become so routine that determining the sequence of a DNA molecule is not inventive.

Response: The comments are not adopted. A DNA sequence is not patentable because a sequence is merely descriptive information about a molecule. An isolated and purified DNA molecule may be patentable because a molecule is a 'composition of matter,' one of the four classes of invention authorized by 35 U.S.C. 101.

A DNA molecule must be *nonobvious* in order to be patentable. Obviousness does not depend on the amount of work required to characterize the DNA molecule. *See* 35 U.S.C. 103(a) ('Patentability shall not be negatived by the manner in which the invention was made.'). As the nonobviousness requirement has been interpreted by the U.S. Court of Appeals for the Federal Circuit, whether a claimed DNA molecule would have been obvious depends on whether a molecule having the particular *structure* of the DNA would have been obvious to one of ordinary skill in the art at the time the invention was made. *See, e.g., In re Deuel,* 51 F.3d 1552, 1559, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995) ('[T]he existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious.'); *see also, In re Bell,* 991 F.2d 781, 26 USPQ2d 1529 (Fed. Cir. 1993)

(14) ***Comment***: One comment suggested that genes ought to be patentable only when the complete sequence of the gene is disclosed and a function for the gene product has been determined.

Response: The suggestion is not adopted. To obtain a patent on a chemical compound such as DNA, a patent applicant must adequately describe the compound and must disclose how to make and use the compound. 35 U.S.C. 101, 112. 'An adequate written description of a DNA * * * requires a precise definition, *such as* by structure, formula, chemical name, or physical properties.' *Univ. of California* v. *Eli Lilly & Co.,* 119 F.3d 1559, 1556, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997) (emphasis added, internal quote omitted). Thus, describing the complete chemical structure, *i.e.,* the DNA sequence, is one method of describing a DNA molecule but it is not the only method. In addition, the utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have a

specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has a gene-regulating activity

(15) ***Comment***: One comment stated that the specification should 'disclose the invention,' including why the invention works and how it was developed.

Response: The comment is not adopted. The comment is directed more to the requirements imposed by 35 U.S.C. 112 than to those of 35 U.S.C. 101. To satisfy the enablement requirement of 35 U.S.C. 112, ¶ 1, an application must disclose the claimed invention in sufficient detail to enable a person of ordinary skill in the art to make and use the claimed invention. To satisfy the written description requirement of 35 U.S.C. 112, ¶ 1, the description must show that the applicant was in possession of the claimed invention at the time of filing. If all the requirements under 35 U.S.C. 112, ¶1, are met, there is no statutory basis to require disclosure of why an invention works or how it was developed. '[I]t is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works.' *Newman* v. *Quigg*, 877 F.2d 1575, 1581, 11 USPQ2d 1340, 1345 (Fed. Cir. 1989)

(16) ***Comment***: One comment suggested that patents should 'allow for others to learn from and improve the invention.' The comment suggested that claims to patented plant varieties should not prohibit others from using the patented plants to develop improved varieties. The comment also stated that uses of plants in speculative manners should not be permitted.

Response: By statute, a patent provides the patentee with the right to exclude others from, *inter alia*, making and using the claimed invention, although a limited research exemption exists. *See* 35 U.S.C. 163, 271(a), (e). These statutory provisions are not subject to revision by the USPTO and are not affected by these Guidelines.

Where a plant is claimed in a utility patent application, compliance with the statutory requirements for utility under 35 U.S.C. 101 only requires that a claimed invention be supported by at least one specific, substantial and credible utility. It is somewhat rare for academic researchers to be sued by commercial patent owners for patent infringement. Most inventions are made available to academic researchers on very favorable licensing terms, which enable them to continue their research.

(17) ***Comment***: Two comments suggested that although the USPTO has made a step in the right direction in raising the bar in the Utility Guidelines, there is still a need to apply stricter standards for utility.

Response: The USPTO is bound by 35 U.S.C. 101 and the case law interpreting § 101. The Guidelines reflect the USPTO's understanding of § 101.

(18) ***Comment***: Several comments addressed specific concerns about the examiner training materials.

Response: The comments received with respect to the training materials will be taken under advisement as the Office revises the training materials. Except for comments with regard to whether sequence homology is sufficient to demonstrate a specific and substantial credible utility, specific concerns about the training materials will not be addressed herein as they will not impact the language of the guidelines.

(19) ***Comment***: Several comments suggested that the use of computer based analysis of nucleic acids to assign a function to a given nucleic acid based upon homology to prior art nucleic acids found in databases is highly unpredictable and cannot form a basis for an assignment of function to a putatively encoded protein. These comments also indicate that even in instances where a general functional assignment may be reasonable, the assignment does not provide information regarding the actual biological activity of an encoded protein and therefore patent claims drawn to such nucleic acids should be limited to method of use claims that are explicitly supported by the as-filed specification(s). These comments also state that if homology-based utilities are acceptable, then the nucleic acids, and proteins encoded thereby, should be considered as obvious over the prior art nucleic acids. On the other hand,

one comment stated that homology is a standard, art-accepted basis for predicting utility, while another comment stated that any level of homology to a protein with known utility should be accepted as indicative of utility.

Response: The suggestions to adopt a *per se* rule rejecting homology based assertions of utility are not adopted. An applicant is entitled to a patent to the subject matter claimed unless statutory requirements are not met (35 U.S.C. 101, 102, 103, 112)

When the USPTO denies a patent, the Office must set forth at least a *prima facie* case as to why an applicant has not met the statutory requirements. The inquiries involved in assessing utility are fact dependent, and the determinations must be made on the basis of scientific evidence. Reliance on the commenters' *per se* rule, rather than a fact dependent inquiry, is impermissible because the commenters provide no scientific evidence that homology-based assertions of utility are inherently unbelievable or involve implausible scientific principles. *See, e.g., In re Brana,* 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (rejection of claims improper where claims did 'not suggest an inherently unbelievable undertaking or involve implausible scientific principles' and where 'prior art * * * discloses structurally similar compounds to those claimed by the applicants which have been proven * * * to be effective')

A patent examiner must accept a utility asserted by an applicant unless the Office has evidence or sound scientific reasoning to rebut the assertion. The examiner's decision must be supported by a preponderance of all the evidence of record. *In re Oetiker,* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). More specifically, when a patent application claiming a nucleic acid asserts a specific, substantial, and credible utility, and bases the assertion upon homology to existing nucleic acids or proteins having an accepted utility, the asserted utility must be accepted by the examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion. '[A] 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' is sufficient.' *Fujikawa* v *Wattanasin,* 93 F.3d 1559, 1565, 39 USPQ2d 1895, 1900 (Fed. Cir. 1996)

The Office will take into account both the nature and degree of the homology. When a class of proteins is defined such that the members share a specific, substantial, and credible utility, the reasonable assignment of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial, and credible utility to the assigned protein. If the preponderance of the evidence of record, or of sound scientific reasoning, casts doubt upon such an asserted utility, the examiner should reject the claim for lack of utility under 35 U.S.C.101. For example, where a class of proteins is defined by common structural features, but evidence shows that the members of the class do not share a specific, substantial functional attribute or utility, despite having structural features in common, membership in the class may not impute a specific, substantial, and credible utility to a new member of the class. When there is a reason to doubt the functional protein assignment, the utility examination may turn to whether or not the asserted protein encoded by a claimed nucleic acid has a well-established use. If there is a well-established utility for the protein and the claimed nucleic acid, the claim would meet the requirements for utility under 35 U.S.C. 101. If not, the burden shifts to the applicant to provide evidence supporting a well-established utility. There is no *per se* rule regarding homology, and each application must be judged on its own merits.

The comment indicating that if a homology-based utility could meet the requirements set forth under 35 U.S.C. 101, then the invention would have been obvious, is not adopted. Assessing nonobviousness under 35 U.S.C. 103 is separate from analyzing the utility requirements under 35 U.S.C. 101. When a claim to a nucleic acid supported by a homology-based utility meets the utility requirement of section 101, it does not follow that the claimed nucleic acid would have been *prima facie* obvious over the nucleic acids to which it is homologous. '[S]ection 103 requires a fact-intensive comparison of the [claim] with the prior art rather than the mechanical application of one or another *per se* rule.' *In re Ochiai,* 71 F.3d 1565, 1571, 37 USPQ2d 1127, 1132 (Fed. Cir. 1995). Nonobviousness must be determined according to the analysis in *Graham* v. *John Deere,* 383 U.S. 1, 148 USPQ 459 (1966). *See also, In re Dillon,* 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (in banc) ('structural similarity between claimed and prior art subject matter, * * * *where the prior art gives reason or motivation to make the claimed compositions,* creates a prima

facie case of obviousness') (emphasis added)

Where 'the prior art teaches a specific, structurally-definable compound [] the question becomes whether the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention.' *In re Deuel,* 51 F.3d 1552, 1558, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995)

(20) ***Comment****:* Several comments indicated that in situations where a well-established utility is relied upon for compliance with 35 U.S.C. 101, the record should reflect what that utility is. One comment stated that the record should reflect whether the examiner accepted an asserted utility or relied upon a well-established utility after dismissing all asserted utilities. Another comment stated that when the examiner relies on a well-established utility not explicitly asserted by the applicant, the written record should clearly identify this utility and the rationale for considering it specific and substantial

Response: The comments are not adopted. Only one specific, substantial and credible utility is required to satisfy the statutory requirement. Where one or more well-established utilities would have been readily apparent to those of skill in the art at the time of the invention, an applicant may rely on any one of those utilities without prejudice

The record of any issued patent typically reflects consideration of a number of references in the prior art that the applicant or the examiner considered material to the claimed invention. These references often indicate uses for related inventions, and any patents listed typically disclose utilities for related inventions. Thus, even when the examiner does not identify a well-established utility, the record as a whole will likely disclose readily apparent utilities. Just as the examiner without comment may accept a properly asserted utility, there is no need for an examiner to comment on the existence of a well-established utility

However, the Guidelines have been revised to clarify that a well-established utility is a specific, substantial, and credible utility that must be readily apparent to one skilled in the art. Most often, the closest prior art cited and applied in the course of examining the application will demonstrate a well-established utility for the invention

(21) ***Comment****:* Several comments stated that the Guidelines erroneously burden the examiner with proving that a person of skill in the art would not be aware of a well-established utility. One comment states that this requires the examiner to prove a negative. Another comment states that the Guidelines should direct examiners that if a specific utility has not been disclosed, the applicant should be required to identify a specific utility.

Response: The comments have been adopted in part. The Guidelines have been revised to indicate that where the applicant has not asserted a specific, substantial, and credible utility, and the examiner does not perceive a well-established utility, a rejection under § 101 should be entered. That is, if a well-established utility is not readily apparent and an invention is not otherwise supported by an asserted specific, substantial, and credible utility, the burden will be shifted to applicant to show either that the specification discloses an adequate utility, or to show that a well-established utility exists for the claimed invention. Again, most often the search of the closest prior art will reveal whether there is a well-established utility for the claimed invention

(22) ***Comment****:* Several comments suggested that further clarification was required with regard to the examiner's determination that there is an adequate nexus between a showing supporting a well-established utility and the application as filed. The comments indicated that the meaning of this 'nexus' was unclear.

Response: The Guidelines have been modified to reflect that evidence provided by an applicant is to be analyzed with regard to a concordance between the showing and the full scope and content of the claimed invention as disclosed in the application as filed. In situations where the showing provides adequate evidence that the claim is supported by at least one asserted specific, substantial, and credible or well-established utility, the rejections under 35 U.S.C. 101 and 112, first paragraph, will be withdrawn. However, the examiner is instructed to consider whether or not the specification, in light of applicant's

showing, is enabled for the use of the full scope of the claimed invention. Many times prior patents and printed publications provided by applicant will clearly demonstrate that a well-established utility exists.

(23) ***Comment***: One comment states that the Office is using an improper standard in assessing 'specific' utility

According to the comment, a distinction between 'specific' and 'general' utilities is an overreaching interpretation of the specificity requirement in the case law because 'unique' or 'particular' utilities have never been required by the law. The comment states that the specificity requirement concerns sufficiency of disclosure, *i.e.*, teaching how to make and use a claimed invention, not the utility requirement. The comment states that the specificity requirement is to be distinguished from the 'substantial' utility requirement, and that the *Brenner* v. *Manson* decision concerned only a 'substantial' utility issue, not specificity.

Response: The comment is not adopted. The disclosure of only a general utility rather than a particular utility is insufficient to meet statutory requirements. Although the specificity requirement is relevant to § 112, it is not severable from the utility requirement. [S]urely Congress intended § 112 to presuppose *full satisfaction* of the requirements of § 101. Necessarily, compliance with § 112 requires a description of how to use presently useful inventions, otherwise an applicant would anomalously be required to teach how to use a useless invention. As this court stated in *Diederich*, quoting with approval from the decision of the board: 'We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.' As the Supreme Court said in Brenner v Manson: '* * * a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.' *In re Kirk*, 376 F.2d 936, 942, 153 USPQ 48, 53 (CCPA 1967) (affirming rejections under §§ 101 and 112) (emphasis in original)

II. Guidelines for Examination of Applications for Compliance With the Utility Requirement

Introduction

The following Guidelines establish the policies and procedures to be followed by Office personnel in the evaluation of any patent application for compliance with the utility requirements of 35 U.S.C. 101 and 112. These Guidelines have been promulgated to assist Office personnel in their review of applications for compliance with the utility requirement. The Guidelines do not alter the substantive requirements of 35 U.S.C. 101 and 112, nor are they designed to obviate the examiner's review of applications for compliance with all other statutory requirements for patentability. The Guidelines do not constitute substantive rulemaking and hence do not have the force and effect of law. Rejections will be based upon the substantive law, and it is these rejections which are appealable. Consequently, any perceived failure by Office personnel to follow these Guidelines is neither appealable nor petitionable

B. Examination Guidelines for the Utility Requirement

Office personnel are to adhere to the following procedures when reviewing patent applications for compliance with the 'useful invention' ('utility') requirement of 35 U.S.C. 101 and 112, first paragraph

1. Read the claims and the supporting written description
(a) Determine what the applicant has claimed, noting any specific embodiments of the invention

(b) Ensure that the claims define statutory subject matter (*i.e.*, a process, machine, manufacture, composition of matter, or improvement thereof)

(c) If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility (1) if a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (*e.g.*, properties or applications of a product or process), and (2) the utility is specific, substantial, and credible

2. Review the claims and the supporting written description to determine if the applicant has asserted for the claimed invention any specific and substantial utility that is credible:

(a) If the applicant has asserted that the claimed invention is useful for any particular practical purpose (*i.e.*, it has a 'specific and substantial utility') and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility

> (1) A claimed invention must have a specific and substantial utility. This requirement excludes 'throw-away,' 'insubstantial,' or 'nonspecific' utilities, such as the use of a complex invention as landfill, as a way of satisfying the utility requirement of 35 U.S.C. 101
> (2) Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record (*e.g.*, test data, affidavits or declarations from experts in the art, patents or printed publications) that is probative of the applicant's assertions. An applicant need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement.

(b) If no assertion of specific and substantial utility for the claimed invention made by the applicant is credible, and the claimed invention does not have a readily apparent well established utility, reject the claim(s) under § 101 on the grounds that the invention as claimed lacks utility. Also reject the claims under § 112, first paragraph, on the basis that the disclosure fails to teach how to use the invention as claimed. The § 112, first paragraph, rejection imposed in conjunction with a § 101 rejection should incorporate by reference the grounds of the corresponding § 101 rejection.

(c) If the applicant has not asserted any specific and substantial utility for the claimed invention and it does not have a readily apparent well-established utility, impose a rejection under § 101, emphasizing that the applicant has not disclosed a specific and substantial utility for the invention. Also impose a separate rejection under § 112, first paragraph, on the basis that the applicant has not disclosed how to use the invention due to the lack of a specific and substantial utility. The §§ 101 and 112 rejections shift the

burden of coming forward with evidence to the applicant to:

(1) Explicitly identify a specific and substantial utility for the claimed invention; and

(2) Provide evidence that one of ordinary skill in the art would have recognized that the identified specific and substantial utility was well established at the time of filing. The examiner should review any subsequently submitted evidence of utility using the criteria outlined above

The examiner should also ensure that there is an adequate nexus between the evidence and the properties of the now claimed subject matter as disclosed in the application as filed. That is, the applicant has the burden to establish a probative relation between the submitted evidence and the originally disclosed properties of the claimed invention.

3. Any rejection based on lack of utility should include a detailed explanation why the claimed invention has no specific and substantial credible utility. Whenever possible, the examiner should provide documentary evidence regardless of publication date (*e.g.*, scientific or technical journals, excerpts from treatises or books, or U.S. or foreign patents) to support the factual basis for the *prima facie* showing of no specific and substantial credible utility. If documentary evidence is not available, the examiner should specifically explain the scientific basis for his or her factual conclusions.

(a) Where the asserted utility is not specific or substantial, a *prima facie* showing must establish that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the applicant would be specific and substantial. The *prima facie* showing must contain the following elements:

(1) An explanation that clearly sets forth the reasoning used in concluding that the asserted utility for the claimed invention is not both specific and substantial nor well-established;

(2) Support for factual findings relied upon in reaching this conclusion; and

(3) An evaluation of all relevant evidence of record, including utilities taught in the closest prior art

(b) Where the asserted specific and substantial utility is not credible, a *prima facie* showing of no specific and substantial credible utility must establish that it is more likely than not that a person skilled in the art would not consider credible any specific and substantial utility asserted by the applicant for the claimed invention.

The *prima facie* showing must contain the following elements:

(1) An explanation that clearly sets forth the reasoning used in concluding that the asserted specific and substantial utility is not credible;

(2) Support for factual findings relied upon in reaching this conclusion; and

(3) An evaluation of all relevant evidence of record, including utilities taught in the closest prior art

(c) Where no specific and substantial utility is disclosed or is well established, a *prima facie* showing of no specific and substantial utility need only establish that applicant has not asserted a utility and that, on the record before the examiner, there is no known well-established utility.

4. A rejection based on lack of utility should not be maintained if an asserted utility for the claimed invention would be considered specific, substantial, and credible by a person of ordinary skill in the art in view of all evidence of record.

Office personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. Similarly, Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered.

Once a *prima facie* showing of no specific and substantial credible utility has been properly established, the applicant bears the burden of rebutting it. The applicant can do this by amending the claims, by providing reasoning or arguments, or by providing evidence in the form of a declaration under 37 CFR 1.132 or a

patent or a printed publication that rebuts the basis or logic of the *prima facie* showing. If the applicant responds to the *prima facie* rejection, the Office personnel should review the original disclosure, any evidence relied upon in establishing the *prima facie* showing, any claim amendments, and any new reasoning or evidence provided by the applicant in support of an asserted specific and substantial credible utility. It is essential for Office personnel to recognize, fully consider and respond to each substantive element of any response to a rejection based on lack of utility. Only where the totality of the record continues to show that the asserted utility is not specific, substantial, and credible should a rejection based on lack of utility be maintained

If the applicant satisfactorily rebuts a *prima facie* rejection based on lack of utility under § 101, withdraw the § 101 rejection and the corresponding rejection imposed under § 112, first paragraph.

Dated: December 29, 2000

Q. Todd Dickinson, *Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office*

Annex Three

EU Biotechnology Directive

Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions

Official Journal L 213 , 30/07/1998 p. 0013 - 0021

DIRECTIVE 98/44/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 July 1998 on the legal protection of biotechnological inventions

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 100a thereof,

Having regard to the proposal from the Commission (1),

Having regard to the opinion of the Economic and Social Committee (2),

Acting in accordance with the procedure laid down in Article 189b of the Treaty (3),

(1) Whereas biotechnology and genetic engineering are playing an increasingly important role in a broad range of industries and the protection of biotechnological inventions will certainly be of fundamental importance for the Community's industrial development;

(2) Whereas, in particular in the field of genetic engineering, research and development require a considerable amount of high-risk investment and therefore only adequate legal protection can make them profitable;

(3) Whereas effective and harmonised protection throughout the Member States is essential in order to maintain and encourage investment in the field of biotechnology;

(4) Whereas following the European Parliament's rejection of the joint text, approved by the Conciliation Committee, for a European Parliament and Council Directive on the legal protection of biotechnological inventions (4), the European Parliament and the Council have determined that the legal protection of biotechnological inventions requires clarification;

(5) Whereas differences exist in the legal protection of biotechnological inventions offered by the laws and practices of the different Member States; whereas such differences could create barriers to trade and hence impede the proper functioning of the internal market;

(6) Whereas such differences could well become greater as Member States adopt new and different legislation and administrative practices, or whereas national case-law interpreting such legislation develops differently;

(7) Whereas uncoordinated development of national laws on the legal protection of biotechnological inventions in the Community could lead to further disincentives to trade, to the detriment of the industrial development of such inventions and of the smooth operation of the internal market;

(8) Whereas legal protection of biotechnological inventions does not necessitate the creation of a separate body of law in place of the rules of national patent law; whereas the rules of national patent law remain the essential basis for the legal protection of biotechnological inventions given that they must be adapted or added to in certain specific respects in order to take adequate account of technological developments involving biological material which also fulfil the requirements for patentability;

(9) Whereas in certain cases, such as the exclusion from patentability of plant and animal varieties and of essentially biological processes for the production of plants and animals, certain concepts in national laws based upon international patent and plant variety conventions have created uncertainty regarding the protection of biotechnological and certain microbiological inventions; whereas harmonisation is necessary to clarify the said uncertainty;

(10) Whereas regard should be had to the potential of the development of biotechnology for the environment and in particular the utility of this technology for the development of methods of cultivation which are less polluting and more economical in their use of ground; whereas the patent system should be used to encourage research into, and the application of, such processes;

(11) Whereas the development of biotechnology is important to developing countries, both in the field of health and combating major epidemics and endemic diseases and in that of combating hunger in the world; whereas the patent system should likewise be used to encourage research in these fields; whereas international procedures for the dissemination of such technology in the Third World and to the benefit of the population groups concerned should be promoted;

(12) Whereas the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPs) (5) signed by the European Community and the Member States, has entered into force and provides that patent protection must be guaranteed for products and processes in all areas of technology;

(13) Whereas the Community's legal framework for the protection of biotechnological inventions can be limited to laying down certain principles as they apply to the patentability of biological material as such, such principles being intended in particular to determine the difference between inventions and discoveries with regard to the patentability of certain elements of human origin, to the scope of protection conferred by a patent on a biotechnological invention, to the right to use a deposit mechanism in addition to written descriptions and lastly to the option of obtaining non-exclusive compulsory licences in respect of interdependence between plant varieties and inventions, and conversely;

(14) Whereas a patent for invention does not authorise the holder to implement that invention, but merely entitles him to prohibit third parties from exploiting it for industrial and commercial purposes; whereas, consequently, substantive patent law cannot serve to replace or render superfluous national, European or international law which may impose restrictions or prohibitions or which concerns the monitoring of research and of the use or commercialisation of its results, notably from the point of view of the requirements of public health, safety, environmental protection, animal welfare, the preservation of genetic diversity and compliance with certain ethical standards;

(15) Whereas no prohibition or exclusion exists in national or European patent law (Munich Convention) which precludes a priori the patentability of biological matter;

(16) Whereas patent law must be applied so as to respect the fundamental principles safeguarding the dignity and integrity of the person; whereas it is important to assert the principle that the human body, at any stage in its formation or development, including germ cells, and the simple discovery of one of its elements or one of its products, including the sequence or partial sequence of a human gene, cannot be patented; whereas these principles are in line with the criteria of patentability proper to patent law, whereby a mere discovery cannot be patented;

(17) Whereas significant progress in the treatment of diseases has already been made thanks to the existence of medicinal products derived from elements isolated from the human body and/or otherwise produced, such medicinal products resulting from technical processes aimed at obtaining elements similar in structure to those existing naturally in the human body and

whereas, consequently, research aimed at obtaining and isolating such elements valuable to medicinal production should be encouraged by means of the patent system;

(18) Whereas, since the patent system provides insufficient incentive for encouraging research into and production of biotechnological medicines which are needed to combat rare or 'orphan' diseases, the Community and the Member States have a duty to respond adequately to this problem;

(19) Whereas account has been taken of Opinion No 8 of the Group of Advisers on the Ethical Implications of Biotechnology to the European Commission;

(20) Whereas, therefore, it should be made clear that an invention based on an element isolated from the human body or otherwise produced by means of a technical process, which is susceptible of industrial application, is not excluded from patentability, even where the structure of that element is identical to that of a natural element, given that the rights conferred by the patent do not extend to the human body and its elements in their natural environment;

(21) Whereas such an element isolated from the human body or otherwise produced is not excluded from patentability since it is, for example, the result of technical processes used to identify, purify and classify it and to reproduce it outside the human body, techniques which human beings alone are capable of putting into practice and which nature is incapable of accomplishing by itself;

(22) Whereas the discussion on the patentability of sequences or partial sequences of genes is controversial; whereas, according to this Directive, the granting of a patent for inventions which concern such sequences or partial sequences should be subject to the same criteria of patentability as in all other areas of technology: novelty, inventive step and industrial application; whereas the industrial application of a sequence or partial sequence must be disclosed in the patent application as filed;

(23) Whereas a mere DNA sequence without indication of a function does not contain any technical information and is therefore not a patentable invention;

(24) Whereas, in order to comply with the industrial application criterion it is necessary in cases where a sequence or partial sequence of a gene is used to produce a protein or part of a protein, to specify which protein or part of a protein is produced or what function it performs;

(25) Whereas, for the purposes of interpreting rights conferred by a patent, when sequences overlap only in parts which are not essential to the invention, each sequence will be considered as an independent sequence in patent law terms;

(26) Whereas if an invention is based on biological material of human origin or if it uses such material, where a patent application is filed, the person from whose body the material is taken must have had an opportunity of expressing free and informed consent thereto, in accordance with national law;

(27) Whereas if an invention is based on biological material of plant or animal origin or if it uses such material, the patent application should, where appropriate, include information on the geographical origin of such material, if known; whereas this is without prejudice to the processing of patent applications or the validity of rights arising from granted patents;

(28) Whereas this Directive does not in any way affect the basis of current patent law, according to which a patent may be granted for any new application of a patented product;

(29) Whereas this Directive is without prejudice to the exclusion of plant and animal varieties from patentability; whereas on the other hand inventions which concern plants or animals are patentable provided that the application of the invention is not technically confined to a single plant or animal variety;

(30) Whereas the concept 'plant variety' is defined by the legislation protecting new varieties, pursuant to which a variety is defined by its whole genome and therefore possesses individuality and is clearly distinguishable from other varieties;

(31) Whereas a plant grouping which is characterised by a particular gene (and not its whole genome) is not covered by the protection of new varieties and is therefore not excluded from patentability even if it comprises new varieties of plants;

(32) Whereas, however, if an invention consists only in genetically modifying a particular plant variety, and if a new plant variety is bred, it will still be excluded from patentability even if the genetic modification is the result not of an essentially biological process but of a biotechnological process;

(33) Whereas it is necessary to define for the purposes of this Directive when a process for the breeding of plants and animals is essentially biological;

(34) Whereas this Directive shall be without prejudice to concepts of invention and discovery, as developed by national, European or international patent law;

(35) Whereas this Directive shall be without prejudice to the provisions of national patent law whereby processes for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body are excluded from patentability;

(36) Whereas the TRIPs Agreement provides for the possibility that members of the World Trade Organisation may exclude from patentability inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect ordre public or morality, including to protect human, animal or plant life or health or to avoid serious prejudice to the environment, provided that such exclusion is not made merely because the exploitation is prohibited by their law;

(37) Whereas the principle whereby inventions must be excluded from patentability where their commercial exploitation offends against ordre public or morality must also be stressed in this Directive;

(38) Whereas the operative part of this Directive should also include an illustrative list of inventions excluded from patentability so as to provide national courts and patent offices with a general guide to interpreting the reference to ordre public and morality; whereas this list obviously cannot presume to be exhaustive; whereas processes, the use of which offend against human dignity, such as processes to produce chimeras from germ cells or totipotent cells of humans and animals, are obviously also excluded from patentability;

(39) Whereas ordre public and morality correspond in particular to ethical or moral principles recognised in a Member State, respect for which is particularly important in the field of biotechnology in view of the potential scope of inventions in this field and their inherent relationship to living matter; whereas such ethical or moral principles supplement the standard legal examinations under patent law regardless of the technical field of the invention;

(40) Whereas there is a consensus within the Community that interventions in the human germ line and the cloning of human beings offends against ordre public and morality; whereas it is therefore important to exclude unequivocally from patentability processes for modifying the germ line genetic identity of human beings and processes for cloning human beings;

(41) Whereas a process for cloning human beings may be defined as any process, including techniques of embryo splitting, designed to create a human being with the same nuclear genetic information as another living or deceased human being;

(42) Whereas, moreover, uses of human embryos for industrial or commercial purposes must also be excluded from patentability; whereas in any case such exclusion does not affect inventions for therapeutic or diagnostic purposes which are applied to the human embryo and are useful to it;

(43) Whereas pursuant to Article F(2) of the Treaty on European Union, the Union is to respect fundamental rights, as guaranteed by the European Convention for the Protection of Human Rights and Fundamental Freedoms signed in Rome on 4 November 1950 and as they result from the constitutional traditions common to the Member States, as general principles of Community law;

(44) Whereas the Commission's European Group on Ethics in Science and New Technologies evaluates all ethical aspects of biotechnology; whereas it should be pointed out in this connection that that Group may be consulted only where biotechnology is to be evaluated at the level of basic ethical principles, including where it is consulted on patent law;

(45) Whereas processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit in terms of research, prevention, diagnosis or therapy to man or animal, and also animals resulting from such processes, must be excluded from patentability;

(46) Whereas, in view of the fact that the function of a patent is to reward the inventor for his creative efforts by granting an exclusive but time-bound right, and thereby encourage inventive activities, the holder of the patent should be entitled to prohibit the use of patented self-reproducing material in situations analogous to those where it would be permitted to prohibit the use of patented, non-self-reproducing products, that is to say the production of the patented product itself;

(47) Whereas it is necessary to provide for a first derogation from the rights of the holder of the patent when the propagating material incorporating the protected invention is sold to a farmer for farming purposes by the holder of the patent or with his consent; whereas that initial derogation must authorise the farmer to use the product of his harvest for further multiplication or propagation on his own farm; whereas the extent and the conditions of that derogation must be limited in accordance with the extent and conditions set out in Council Regulation (EC) No 2100/94 of 27 July 1994 on Community plant variety rights (6);

(48) Whereas only the fee envisaged under Community law relating to plant variety rights as a condition for applying the derogation from Community plant variety rights can be required of the farmer;

(49) Whereas, however, the holder of the patent may defend his rights against a farmer abusing the derogation or against a breeder who has developed a plant variety incorporating the protected invention if the latter fails to adhere to his commitments;

(50) Whereas a second derogation from the rights of the holder of the patent must authorise the farmer to use protected livestock for agricultural purposes;

(51) Whereas the extent and the conditions of that second derogation must be determined by national laws, regulations and practices, since there is no Community legislation on animal variety rights;

(52) Whereas, in the field of exploitation of new plant characteristics resulting from genetic engineering, guaranteed access must, on payment of a fee, be granted in the form of a compulsory licence where, in relation to the genus or species concerned, the plant variety represents significant technical progress of considerable economic interest compared to the invention claimed in the patent;

(53) Whereas, in the field of the use of new plant characteristics resulting from new plant varieties in genetic engineering, guaranteed access must, on payment of a fee, be granted in the form of a compulsory licence where the invention represents significant technical progress of considerable economic interest;

(54) Whereas Article 34 of the TRIPs Agreement contains detailed provisions on the burden of proof which is binding on all Member States; whereas, therefore, a provision in this Directive is not necessary;

(55) Whereas following Decision 93/626/EEC (7) the Community is party to the Convention on Biological Diversity of 5 June 1992; whereas, in this regard, Member States must give particular weight to Article 3 and Article 8(j), the second sentence of Article 16(2) and Article 16(5) of the Convention when bringing into force the laws, regulations and administrative provisions necessary to comply with this Directive;

(56) Whereas the Third Conference of the Parties to the Biodiversity Convention, which took place in November 1996, noted in Decision III/17 that 'further work is required to help develop a common appreciation of the relationship between intellectual property rights and the relevant provisions of the TRIPs Agreement and the Convention on Biological Diversity, in particular on issues relating to technology transfer and conservation and sustainable use of biological diversity and the fair and equitable sharing of benefits arising out of the use of genetic resources, including the protection of knowledge, innovations and practices of indigenous and local communities embodying traditional lifestyles relevant for the conservation and sustainable use of biological diversity',

HAVE ADOPTED THIS DIRECTIVE:

CHAPTER I Patentability

Article 1

1. Member States shall protect biotechnological inventions under national patent law. They shall, if necessary, adjust their national patent law to take account of the provisions of this Directive.

2. This Directive shall be without prejudice to the obligations of the Member States pursuant to international agreements, and in particular the TRIPs Agreement and the Convention on Biological Diversity.

Article 2

1. For the purposes of this Directive,

(a) 'biological material' means any material containing genetic information and capable of reproducing itself or being reproduced in a biological system;

(b) 'microbiological process' means any process involving or performed upon or resulting in microbiological material.

2. A process for the production of plants or animals is essentially biological if it consists entirely of natural phenomena such as crossing or selection.

3. The concept of 'plant variety' is defined by Article 5 of Regulation (EC) No 2100/94.

Article 3

1. For the purposes of this Directive, inventions which are new, which involve an inventive step and which are susceptible of industrial application shall be patentable even if they concern a product consisting of or containing biological material or a process by means of which biological material is produced, processed or used.

2. Biological material which is isolated from its natural environment or produced by means of a technical process may be the subject of an invention even if it previously occurred in nature.

Article 4

1. The following shall not be patentable:

(a) plant and animal varieties;

(b) essentially biological processes for the production of plants or animals.

2. Inventions which concern plants or animals shall be patentable if the technical feasibility of the invention is not confined to a particular plant or animal variety.

3. Paragraph 1(b) shall be without prejudice to the patentability of inventions which concern a microbiological or other technical process or a product obtained by means of such a process.

Article 5

1. The human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions.

2. An element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element.

3. The industrial application of a sequence or a partial sequence of a gene must be disclosed in the patent application.

Article 6

1. Inventions shall be considered unpatentable where their commercial exploitation would be contrary to ordre public or morality; however, exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation.

2. On the basis of paragraph 1, the following, in particular, shall be considered unpatentable:

(a) processes for cloning human beings;

(b) processes for modifying the germ line genetic identity of human beings;

(c) uses of human embryos for industrial or commercial purposes;

(d) processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes.

Article 7

The Commission's European Group on Ethics in Science and New Technologies evaluates all ethical aspects of biotechnology.

CHAPTER II Scope of protection

Article 8

1. The protection conferred by a patent on a biological material possessing specific characteristics as a result of the invention shall extend to any biological material derived from that biological material through propagation or multiplication in an identical or divergent form and possessing those same characteristics.

2. The protection conferred by a patent on a process that enables a biological material to be produced possessing specific characteristics as a result of the invention shall extend to biological material directly obtained through that process and to any other biological material derived from the directly obtained biological material through propagation or multiplication in an identical or divergent form and possessing those same characteristics.

Article 9

The protection conferred by a patent on a product containing or consisting of genetic information shall extend to all material, save as provided in Article 5(1), in which the product in incorporated and in which the genetic information is contained and performs its function.

Article 10

The protection referred to in Articles 8 and 9 shall not extend to biological material obtained from the propagation or multiplication of biological material placed on the market in the territory of a Member State by the holder of the patent or with his consent, where the multiplication or propagation necessarily results from the application for which the biological material was marketed, provided that the material obtained is not subsequently used for other propagation or multiplication.

Article 11

1. By way of derogation from Articles 8 and 9, the sale or other form of commercialisation of plant propagating material to a farmer by the holder of the patent or with his consent for agricultural use implies authorisation for the farmer to use the product of his harvest for propagation or multiplication by him on his own farm, the extent and conditions of this derogation corresponding to those under Article 14 of Regulation (EC) No 2100/94.

2. By way of derogation from Articles 8 and 9, the sale or any other form of commercialisation of breeding stock or other animal reproductive material to a farmer by the holder of the patent or with his consent implies authorisation for the farmer to use the protected livestock for an agricultural purpose. This includes making the animal or other animal reproductive material available for the purposes of pursuing his agricultural activity but not sale within the framework or for the purpose of a commercial reproduction activity.

3. The extent and the conditions of the derogation provided for in paragraph 2 shall be determined by national laws, regulations and practices.

CHAPTER III Compulsory cross-licensing

Article 12

1. Where a breeder cannot acquire or exploit a plant variety right without infringing a prior patent, he may apply for a compulsory licence for non-exclusive use of the invention protected by the patent inasmuch as the licence is necessary for the exploitation of the plant variety to be protected, subject to payment of an appropriate royalty. Member States shall provide that, where such a licence is granted, the holder of the patent will be entitled to a cross-licence on reasonable terms to use the protected variety.

2. Where the holder of a patent concerning a biotechnological invention cannot exploit it without infringing a prior plant variety right, he may apply for a compulsory licence for non-exclusive use of the plant variety protected by that right, subject to payment of an appropriate royalty. Member States shall provide that, where such a licence is granted, the holder of the variety right will be entitled to a cross-licence on reasonable terms to use the protected invention.

3. Applicants for the licences referred to in paragraphs 1 and 2 must demonstrate that:

(a) they have applied unsuccessfully to the holder of the patent or of the plant variety right to obtain a contractual licence;

(b) the plant variety or the invention constitutes significant technical progress of considerable economic interest compared with the invention claimed in the patent or the protected plant variety.

4. Each Member State shall designate the authority or authorities responsible for granting the licence. Where a licence for a plant variety can be granted only by the Community Plant Variety Office, Article 29 of Regulation (EC) No 2100/94 shall apply.

CHAPTER IV Deposit, access and re-deposit of a biological material

Article 13

1. Where an invention involves the use of or concerns biological material which is not available to the public and which cannot be described in a patent application in such a manner as to enable the invention to be reproduced by a person skilled in the art, the description shall be considered inadequate for the purposes of patent law unless:

(a) the biological material has been deposited no later than the date on which the patent application was filed with a recognised depositary institution. At least the international depositary authorities which acquired this status by virtue of Article 7 of the Budapest Treaty of 28 April 1977 on the international recognition of the deposit of micro-organisms for the purposes of patent procedure, hereinafter referred to as the 'Budapest Treaty', shall be recognised;

(b) the application as filed contains such relevant information as is available to the applicant on the characteristics of the biological material deposited;

(c) the patent application states the name of the depository institution and the accession number.

2. Access to the deposited biological material shall be provided through the supply of a sample:

(a) up to the first publication of the patent application, only to those persons who are authorised under national patent law;

(b) between the first publication of the application and the granting of the patent, to anyone requesting it or, if the applicant so requests, only to an independent expert;

(c) after the patent has been granted, and notwithstanding revocation or cancellation of the patent, to anyone requesting it.

3. The sample shall be supplied only if the person requesting it undertakes, for the term during which the patent is in force:

(a) not to make it or any material derived from it available to third parties; and

(b) not to use it or any material derived from it except for experimental purposes, unless the applicant for or proprietor of the patent, as applicable, expressly waives such an undertaking.

4. At the applicant's request, where an application is refused or withdrawn, access to the deposited material shall be limited to an independent expert for 20 years from the date on which the patent application was filed. In that case, paragraph 3 shall apply.

5. The applicant's requests referred to in point (b) of paragraph 2 and in paragraph 4 may only be made up to the date on which the technical preparations for publishing the patent application are deemed to have been completed.

Article 14

1. If the biological material deposited in accordance with Article 13 ceases to be available from the recognised depositary institution, a new deposit of the material shall be permitted on the same terms as those laid down in the Budapest Treaty.

2. Any new deposit shall be accompanied by a statement signed by the depositor certifying that the newly deposited biological material is the same as that originally deposited.

CHAPTER V Final provisions

Article 15

1. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive not later than 30 July 2000. They shall forthwith inform the Commission thereof.

When Member States adopt these measures, they shall contain a reference to this Directive or shall be accompanied by such reference on the occasion of their official publication. The methods of making such reference shall be laid down by Member States.

2. Member States shall communicate to the Commission the text of the provisions of national law which they adopt in the field covered by this Directive.

Article 16

The Commission shall send the European Parliament and the Council:

(a) every five years as from the date specified in Article 15(1) a report on any problems encountered with regard to the relationship between this Directive and international agreements on the protection of human rights to which the Member States have acceded;

(b) within two years of entry into force of this Directive, a report assessing the implications for basic genetic engineering research of failure to publish, or late publication of, papers on subjects which could be patentable;

(c) annually as from the date specified in Article 15(1), a report on the development and implications of patent law in the field of biotechnology and genetic engineering.

Article 17

This Directive shall enter into force on the day of its publication in the Official Journal of the European Communities.

Article 18

This Directive is addressed to the Member States.

Done at Brussels, 6 July 1998.

For the European Parliament The President J. M. GIL-ROBLES

For the Council The President R. EDLINGER

(1) OJ C 296, 8.10.1996, p. 4 and OJ C 311, 11.10.1997, p. 12.

(2) OJ C 295, 7.10.1996, p. 11.

(3) Opinion of the European Parliament of 16 July 1997 (OJ C 286, 22.9.1997, p. 87). Council Common Position of 26 February 1998 (OJ C 110, 8.4.1998, p. 17) and Decision of the European Parliament of 12 May 1998 (OJ C 167, 1.6.1998). Council Decision of 16 June 1998.

(4) OJ C 68, 20.3.1995, p. 26.

(5) OJ L 336, 23.12.1994, p. 213.

(6) OJ L 227, 1.9.1994, p. 1. Regulation as amended by Regulation (EC) No 2506/95 (OJ L 258, 28.10.1995, p. 3).

(7) OJ L 309, 31.12.1993, p. 1.