MACROFIL (EXTERNAL REVIEW)

APOC

Macrofil Review

REVIEW OF MACROFIL

Executive summary

❶ A macrofilaricide has not been developed. But OCT/MACROFIL has made important contributions to drug discovery and development for filarial infections.

❷ MACROFIL has greatly improved drug storage and delivery, drug testing and evaluation and brought these to international GCP/GLP (Good Clinical Practice/Good Laboratory Practice) standards.

❸ There is a continued need for a macrofilaricide for *Onchocerca volvulus* and lymphatic filariasis. There is also a need for a back up or replacement microfilaricide to sustain the OCP achievements.

❹ Development of ivermectin resistance by *Onchocerca volvulus* is a distinct possibility. Therefore resurgences of onchocerciasis in OCP control areas should be monitored and active research into the molecular basis of ivermectin resistance should be continued.
Any use of anthelmintics for filariasis must take into account possible selection for resistance in human gastrointestinal nematodes.

❺ A much greater number of compounds should be screened. In the short term a new microscreen with parasitic nematodes might enable this target to be met. Later this will be met with molecular targets.

❻ Where claims of anthelmintic activity have been made into the scientific literature, every effort should be made to obtain the compounds from the author or other sources.

❼ A full time manager based in Geneva is still required.

❽ Partnership with industry should be encouraged.

❾ The proposal for a drug development unit of the TDR to include MACROFIL is endorsed: research and development plans for a new macrofilaricidal or microfilaricidal compounds should clearly delineate the anticipated profile of the product, including its spectrum of activity, its indications, its level of efficacy and safety, its formulation and dosing, and the costs of application.

1. Review group

Professor D.W.Büttner, Hamburg, Germany.
Dr.G.C.Coles, Bristol, UK (Rapporteur)
Professor D.Stürchler, Liebefeld, Switzerland (Chairperson),
Dr .A.Venkateswarlu, Hyderabad, India.

2. Primary objectives of MACROFIL.

MACROFIL was established with the objective of accelerating the discovery and development of a safe and effective drug for filariasis which will meet the following criteria:
a) the drug must kill or permanently sterilize the adult female worms of *Onchocerca volvulus* without causing allergic reactions in recipients from microfilaricidal action. It must be safe under normal conditions of use when given orally or intramuscularly, be of low cost and be effective in a small number of doses.
b) If the drug has microfilaricidal action, it should be of long duration and reaction in the host should be minimal.

In 1990 the various committees governing OCP and TDR agreed that OCT and the chemotherapy component of TDR filariasis should be amalgamated to form a new project "MACROFIL" devoted solely to the development of macrofilaricides for both onchocercariasis and lymphatic filariasis. The agreement extended the objective to lymphatic filariasis and limited the development of a macrofilaricide, since ivermectin fulfilled the demand for a satisfactory microfilaricide.

OCP was successful with vector control but for recrudescences chemotherapy is needed. Financially OCP will end in 2002. However to sustain the control achieved chemotherapy may have to be extended for another 10-20 years longer. Outside OCP mass treatment all over Africa will be organized by APOC (African Programme for Onchocerciasis Control). This is planned until 2007. The WHO is planning to eliminate both onchocerciasis and filariasis as public health problems. Both sustaining the work of OCP and the decision to eliminate the disease need better drugs which will have to be produced by MACROFIL.

The committee was asked to review the following points (see appendix for full statement).

2.1 Accomplishments and effectiveness

The original objective was to develop a macrofilaricide. This was not reached.

However, MACROFIL has contributed significantly to help characterize ivermectin, to create an environment of partnership between industry and OCT and itself, to set up preclinical and clinical test methods and to evaluate a number of compounds (see appendix) particularly amocarzine and the benzimidazoles.

Ivermectin was developed outside WHO, but OCT/MACROFIL contributed to its success. Ivermectin was registered in 1987 with the participation of Merck & Co and OCT. A major success was persuading MSD to donate the drug and this created a better atmosphere for dealing with industry. Ivermectin has transformed the control of onchocerciasis as it is microfilaricidal with a much less severe Mazzotti reaction than DEC, and it strongly reduces the production of microfilariae by the female worm for 2-10 months. Further work showed that it had a broad therapeutic index permitting its use by inexperienced people. This has paved the way for its widespread use in public health and in the elimination of the pathology of onchocerciasis. However the committee considers that OCP should have followed up women unwittingly dosed in the first 4 months of pregnancy to confirm that it is safe for use in this group. TDR should study this via the women's program.

Ivermectin is also important in *Wuchereria* where it reduces transmission. Thus the work of MACROFIL paved the way for WHO studies on the field delivery of drugs and applied field research.

MACROFIL has also sponsored valuable research on the role of albendazole in reducing microfilariae (it is superior to DEC (diethyl carbamazine)/metrifonate as it is embryocidal) and supported the development of the depot benzimidazole UMF 078. This compound is the current lead. About 1 in 100 active compounds with macro- or microfilaricidal activity can be expected to successfully complete the full research (including galenic, pharmacological and toxicological studies) and development (phases 1 to 3) process up to registration and introduction. Failures with research on leads from Ciba, Upjohn and Wellcome are not therefore surprising and MACROFIL is commended for accepting failures and stopping research on these areas. For example the Ciba-Geigy compound amocarzine (CG 6140) has been dropped for onchocerciasis but is being continued for lymphatic filariasis.

Other major contributions of MACROFIL include:
i] Arranging a data base of chemicals,
ii] Arranging reliable storage and shipping of samples and supply of information on drugs,
iii] Introducing legal contracts between WHO and industry,
iv] Ensuring TDR is becoming more professional in drug development,
v] Setting up clinical centers in Africa and Asia. Especially commended is Dr.Awadzi in Ghana who has produced more than 20 research papers since the last external review in 1987,
vi] Arranging monitoring of clinical centers and drug analytical centers to ensure that the work meets GCP/GLP standards,
vii] Developed standards for assessing damage to adult *O.volvulus* worms by drugs,
viii] Installed a macrodiagnostics laboratory which has proved successful in lymphatic filariasis.
About 200 original research papers produced through MACROFIL sponsorship have had a catalytic effect on research in this area.

The committee was very impressed by all the work that Dr.Ginger has personally undertaken to achieve these targets and results and commend him for his success in the program.

It is clear from the achievements that MACROFIL has been very effective in promoting the development of treatments, and in encouraging research on filarial nematodes. But the committee considers that a change in management structure (2.6) as proposed in the internal review would be beneficial to the program. <u>In addition there must be a much greater testing of novel compounds.</u>

2.2 Future Research Strategy

The committee considered that there is a continued strong need for macrofilaricidal drugs for both onchocerciasis and filariasis.

2.2.1 Risk assessment

Only three broad spectrum groups of anthelmintics (anti-nematodal drugs) have been produced by industry in the last forty years, the benzimidazoles, levamisole/morantel and the

avermectins/milbemycins. At least in part this reflects the need for a new anthelmintic to be better than the predecessors. However, this does not apply to a macrofilaricidal drug where there is no standard to beat. A narrow spectrum anthelmintic that killed adult filarial nematodes would be acceptable. Since there are novel anthelmintic drugs under investigation in the pharmaceutical industry, the chances of finding a novel macrofilaricide are not unreasonable.

2.2.2. Moxidectin

Moxidectin is a successful veterinary product which is more lipophilic than ivermectin. It could, therefore, be more effective in sterilizing female filarial nematodes than ivermectin. The committee supports MACROFILs plan to investigate moxidectin.

2.2.3 Clinical centers

The establishment of quality clinical centers is commended. The committee suggests that for clinical trials on *O.volvulus* the existing center should accept patients from outside the OCP area in order to assess macrofilaricidal activity.

2.2.4 Prophylatic use of filaricides

Whether this should be adopted depends on the chemical entity to be used and the frequency of use. Current compounds of interest are from chemical groups that are also used for control of gastrointestinal nematodes in humans. Frequent use of chemicals is recognized as major cause of selection for resistance particularly when used in the dry season when there are few or no free living stages and all worms in treated people are exposed to drug. In planning the use of anthelmintics for control of filariasis, their possible impact on the development of resistance in gastrointestinal nematodes must be taken into account. However if a chemical with a different mechanism of action was developed and it is not used for gastro-intestinal nematode control it could be used for prophylaxis, if there was a reliable method of distribution .

2.2.5 Potential for ivermectin resistance

Parasitic nematodes have a great genetic diversity. It would therefore be surprising if there are not filarial nematodes that show a reduced response to ivermectin. It is possible that the small numbers of microfilariae that are still produced after ivermectin treatment could represent worms with reduced susceptibility. Existing *in vitro* tests are most unlikely to be able to detect any minor changes in susceptibility of this type. In veterinary nematodes ivermectin analogues have to be used rather than ivermectin and current information suggests tests do not give a good indication of the degree of resistance. The encouraging fact is that in veterinary nematodes genes for ivermectin resistance appear to be rare and intensive use of ivermectin over relatively long periods of time usually appears to be required for clinical problems to emerge. Where ivermectin resistance has arisen relatively fast, numerous doses have been given over a short period.

Two approaches to monitor for resistance could be adopted.
A. Wherever resurgences of onchocerciasis occur within the OCP control area the effectiveness of ivermectin in reducing the filarial burden and in keeping the burden low for as long would be expected should be established. The latter statement is based on the finding that the first sign of resistance in veterinary nematodes can be a reduced egg reappearance period. Any validation of PCR probes for the detection of resistance will require the identification of a population of filariae showing reduced response to ivermectin.
B. The molecular basis of ivermectin resistance in populations of different species of veterinary nematodes should be established. There is an active program to produce PCR probes to detect ivermectin resistance supported by MACROFIL These will be of considerable value for use in the field and the committee therefore fully endorses this work. Obviously as soon as a molecular basis of resistance has been established research must be undertaken to see if the same mechanism could occur in *Onchocerca.*

If albendazole is to be used regularly in the control of filariae, use should be made of existing knowledge of the molecular basis of low level benzimidazole resistance in veterinary nematodes to establish whether this change could occur in filarial nematodes. It should be determined whether a small percentage of worms already have the mutation at amino acid position 200.

The chances that filarial nematodes will develop resistance to ivermectin cannot be predicted. But there have been so many examples of resistance developing to excellent drugs in other parasites that it must be assumed that ivermectin resistance will develop. The committee therefore concluded that a back up or replacement microfilaricide should be sought.

2.3 Current methodology.

Screening has been improved, for example with the inclusion of *in vitro* tests with the target organism where relevant and a switch from *O.gibsoni* to *O.ochengi* for tertiary screening. These techniques using filariae have to be continued for compounds that have shown any nematocidal efficacy. However they are not suitable for primary screening of large numbers of compounds, of unknown potential activity against nematodes. Therefore further attempts should be made to develop an assay using filarial nematodes for testing of large numbers of compounds.

As long as such a test is not available consideration should be given to the introduction of a high throughput assay using other nematodes such as the adult stage of the free living nematode *Caenorhabditis elegans* or larvae of parasitic nematodes such as *Haemonchus contortus* from sheep using a micro developmental assay as used for detecting anthelmintic resistance.

With the chances of a new drug being found estimated at around one per 10,000 compounds tested it is clear that **a much higher rate of screening of compounds must be achieved** if a novel macrofilaricide is to be discovered. Current testing is only running at about 1,000 compounds per year although it is recognized that these are usually molecules that have been preselected for potential activity rather than strictly random. Since it is accepted that there is no satisfactory high throughput screen that is likely to be developed using filarial nematodes in the near future, two alternatives are proposed:

1. All the major leads being worked on have arisen from chemical series having activity against veterinary nematodes. A simple high throughput screen using a veterinary nematode in a 96 well plate should be considered.

2 An alternative approach is using expressed filarial nematode enzymes or receptors in robotic testing systems now being used in the pharmaceutical industry. The committee considered that this approach must be adopted to fit in with methods being used in industry, but recognized that producing an expressed filarial protein was an expensive and time consuming process . It would take several years to obtain a small collection of filarial molecules. Even then the percentage of potential targets being used would be small.

The committee suggests a number of approaches should be undertaken:
a. Asking companies to supply compounds to be tested (*e.g.* in microwell plates for the parasitological test).
b. Literature searches and requesting of compounds. Particular attention must be paid to claims of anthelmintic activity. Where authors will not supply examples, attempts should be made to obtain these from other sources, *e.g.* paraherquamide was not supplied by Merck and Co..
c. Alternate sources of compound should be approached *e.g.* Russia.
d. Advertisements should be placed for compounds in some scientific periodicals (e.g. Chemistry in Britain and Chemical Engineering News) and if necessary some payments made.
e When appropriate, filarial target molecules should be supplied to companies for inclusion in robotic testing.
f. WHO may also consider the approaches followed by the National Cancer Institute, NIH, Bethesda, which has been highly successful in sourcing thousands of compounds from around the world for evaluation in anticancer/anti HIV/ anti-viral screens at NIH.
It was recognized that most of the approaches should be made as a TDR initiative so that all requirements for novel compounds for other screens are included.

With the increase in testing being recommended it is considered that:
i] those compounds showing activity on a high throughput parasitic nematode screen should be tested against filarial nematodes. Whilst his may slightly reduce the chances of finding a lead, it is considered that the diversion of effort into high throughput screening will greatly enhance the chances of drug discovery.
ii] Resistant isolates of *Haemonchus* could be used on active compounds to look for common modes of action. Resistance in a parasitic nematode is likely to be more relevant than those in *C.elegans*, as already recognized in MACROFIL sponsored research on ivermectin resistance.
iii] Compounds found active by robotic testing on filarial target molecules should be tested *in vitro* on both parasitic nematodes and filarial nematodes.

The greatly increased throughput of compounds in screens does not diminish the need to attempt a rational basis of drug design. Identification of putative targets would result in their expression and inclusion into robotic screening. Putative targets might be identified by studying novel compounds showing new types of anthelmintic resistance *e.g.*paraherquamide.

2.4 Financial and human resources

The overall total budget since 1982 of US$29 million available to MACROFIL should be viewed against pharmaceutical industry standards which quote costs for the development of a novel drug in the order of $300 million. Given the financial limits, the committee agrees with a broad proportion of 1/3 of the budget being spent on the identification of new targets and drug screening and of 2/3 spent on preclinical development of an active compound, clinical trials and on research on ivermectin resistance. However, this broad pattern may change rapidly as specific interests or developments occur during the year.

As for manpower the committee is of the strong opinion that a full time manager should continue to be available to MACROFIL. This manager should be based in Geneva because of his or her close cooperation with academia, industry and as a member of product development at WHO. A pre-requisite for clinical trial monitor provided by the product development unit of TDR should be the knowledge and interest in filariasis. The committee recognized the use of recently retired people from industry and endorses this action.

2.5 Partnerships with industry and academia

Over the years MACROFIL has significantly contributed to improved relationships with industry. Model contracts are now available to contract out specific portions of the research or development process. It was felt that well defined tasks, such as, for example, production or toxicity testing, would have a greater chance to attract the interests of industry than large and complete programs with a relatively high risk of failure.

There was a strong case for sharing certain projects with others *e.g.* the European Union and NGOs. The successful joint funding of the *O.ochengi* project should stimulate the search for other partners.

2.6 MACROFIL reporting and line management

The committee welcomes the organizational changes within TDR and the incorporation of MACROFIL into the line management of the planned drug development unit of TDR. However care should be taken that the project manager of MACROFIL does not report to two or more different scientific and technical review committees. To simplify procedures the committee proposes that a common and standardized reporting format be agreed by all responsible committees, and that apart from technical review within TDR, overseeing committees would not review the status more than once per year.

20. Mai 1997

Signed:

Professor D.Stürchler, Chairperson

Dr.G.C.Coles, Rapporteur

Professor D.W.Büttner

Dr.A.Venkateswarlu

ANNEX

1. Structure of a new look TDR/TDP

This was endorsed by the committee.

2. Summary of compound development by MACROFIL.

3. MACROFIL drug screening.

The committee considered that a high throughput screen using nematodes that required a small quantity of chemicals should be put in the plan. Compounds active on this screen should be tested using filarial nematodes. The existing plan requires modification.

4. Objectives and terms of reference

The overall objective of the Review will be to assess the present research and development activities of MACROFIL in the light of its objective to develop a macrofilaricide for use in public health programs before OCP comes to an end in 2002, and to make proposals on a research strategy for the future with particular attention to its cost effectiveness. The following Terms of Reference will apply:

2.1. the Review will assess the research progress to date (effectiveness and accomplishments). The potential and the time frame for the development of a macrofilaricide, and broadly describe the risks involved;

2.2. with emphasis on the future research strategy, the review will assess the desirability and feasibility of any prophylactic use of filaricides, the potential of ivermectin resistance, the need for diagnostic tools to detect such resistance and any possible need for a back-up or replacement microfilaricide;

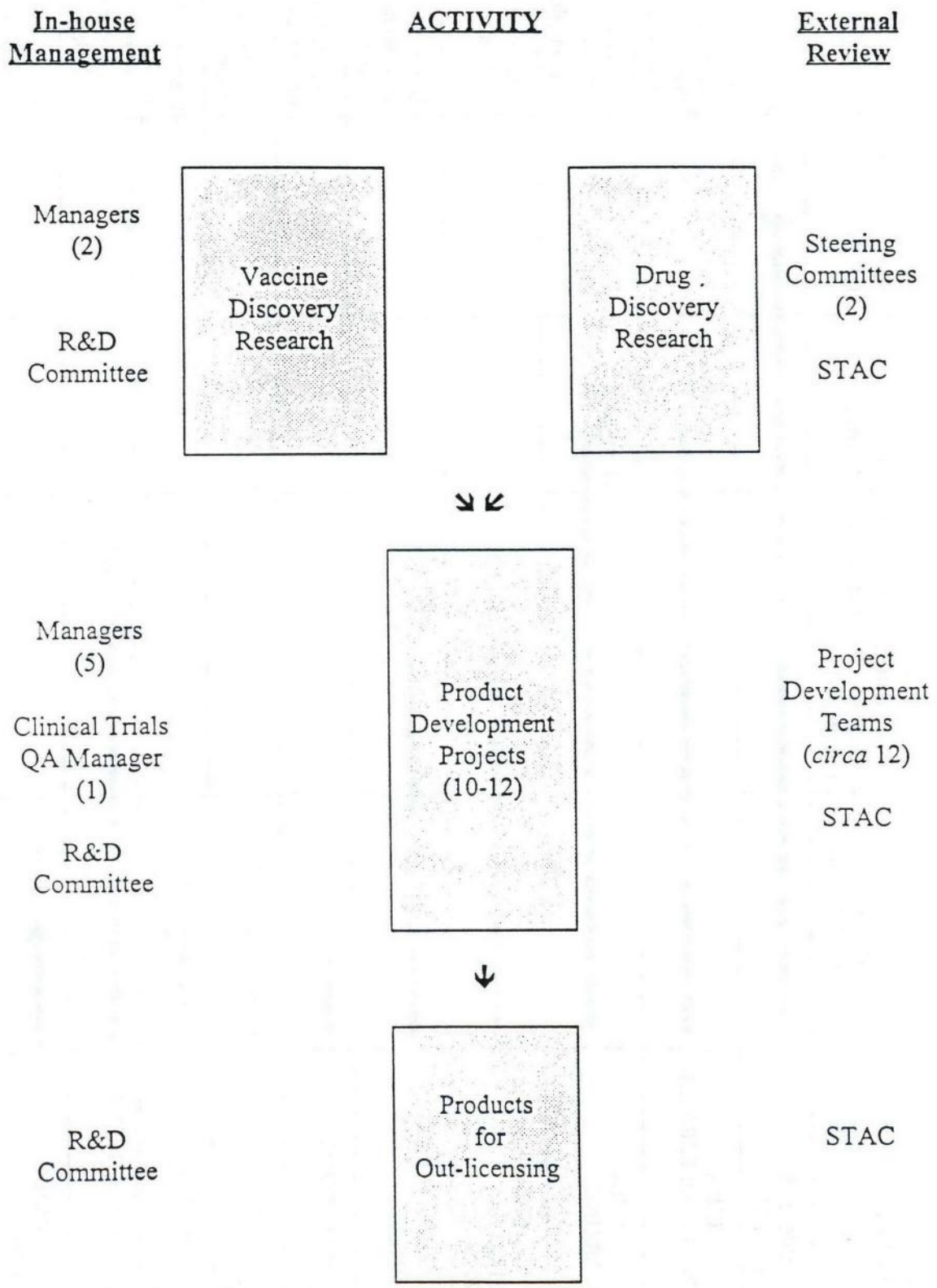
2.3. the Review will evaluate the current methodology of MACROFIL and focus on potential ways of improving that methodology and rendering it more cost-effective, in particular new technologies for compound screening;

2.4. the Review will make proposals on the level of financial support required and the most efficient organization of MACROFIL, bearing in mind that the overall budget for the project is constrained to the range of US$ 2 million per annum;

2.5. the Review will consider whether alternative sources of funding, including the development of partnership with the private sector, should be sought.

2.6 Taking into account that MACROFIL will be financed by three programs, the Review will consider the most appropriate reporting relationship/line management for, and location of, the project manager.

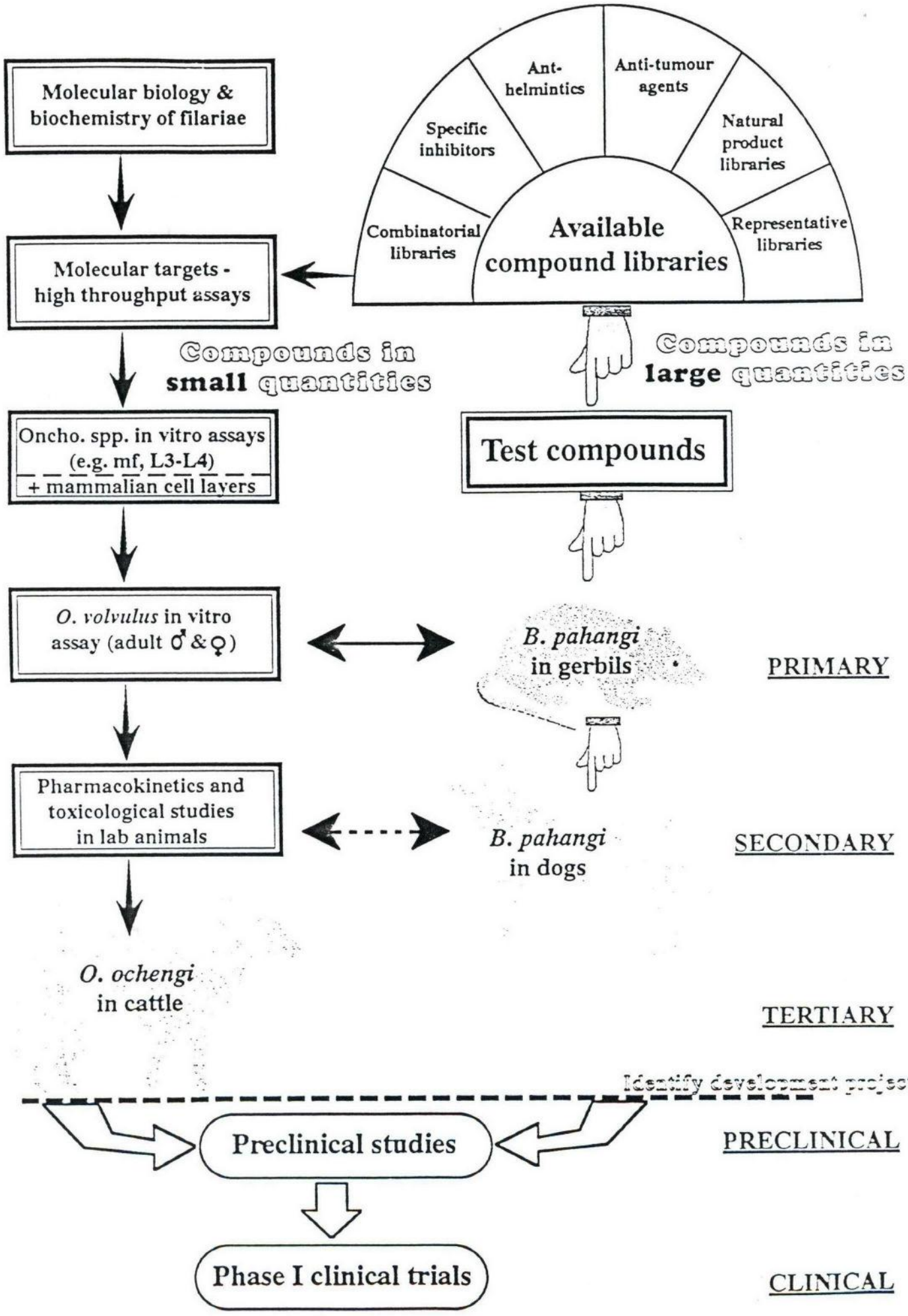
STRUCTURE OF A NEW LOOK TDR/TDP



*List of abbreviations is on page 8

COMPOUND	TERTIARY ASSAYS EFFICACY and/or TOXICITY PROBLEMS	PRECLINICAL TOXICITY OR PHARMACOKINETIC PROBLEMS	CLINICAL TRIALS	REGISTERED FOR USE IN FIELD	REASONS FOR TERMINATION
MERCK & CO. IVERMECTIN				1987	.
CIBA CGP 20376 (with TDR/FIL)			W.bancrofti 1990		Hepatic toxicity at doses lower than required for efficacy. CNS toxicity in dogs
CIBA AMOCARZINE			O.volvulus 1996		Narrow therapeutic index. No efficacy at maximum tolerated dose in Ghana.
CIBA CGP 21833 & CGP 20309		1991			Unacceptable effects on CNS in rodents.
CIBA (INDIA) CGI 18041		1993			Active in primates. Irreversible anaemia in dogs during 28-day studies.
WELLCOME A276C	1989				Toxicity in dogs at doses giving no efficacy.
LILLY 269017	1996				Lead compound toxic in dogs. Analogs showed no efficacy.
WRAIR WR 129577	1997				Inactive in O.ochengi/cattle model.
UNIV. OF MICHIGAN UMF 078		1997			Awaits completion of preclinical toxicology.
WRAIR WR 251993	1997				Inactive in O.ochengi/cattle model. Awaits PK studies on sera.
PARKE-DAVIS PD 105666	1997				Awaits assay in O.ochengi/cattle model.

MACROFIL - Drug Screening



STATUS OF EAC MEMBERSHIP

As at 1 June 1997

Name	First Appointed	Most recent extension (if any)	Last EAC attendance under current appointment	Nationality	Speciality
Abiose	92	09.96	98	Nigeria	-ophthalmology -ivermectin distribution
Asamoa-Baah	96	09.96	98	Ghana	-health plg. -health ecnmcs.
Calamari	92	09.96	98	Italy	-ecology -toxicology
Makubalo	96	09.96	98	Zambia	-community hlth. -epidemiology -educ.psycology
Molyneux	88	09.96	98	U.K	-expertice in most EAC subjects
Prod'hon	93	10.95	97	France	-ivermectin distribution
Tanner	96	09.96	98	Switzerland	-epidemiology -parasitology
Traoré	96	11.96	98	Mali	-social science -epidemiology -community hlth.
Walsh	93	10.95	97	U.K.	-vector control -ivermectin distribution
Yumkella	96	11.96	98	Sierra Leone	-training in health

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Correspondents / Participants

Subject / Title
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Additional Comments

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1) WHO (OCP)
2) Macrof. I review

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Direct: 791 3818

In reply please refer to:
Prière de rappeler la référence: O80/181/1

Your reference:
Votre référence:

Dr Mervyn J. Turner
Senior Vice President
Basic Research
Mail Drop R80K
Merck Research Laboratory
Rahway, N.J. 07965-0900
USA

4 February 1997

Dear Dr Turner,

... I am enclosing an invitation from Mr Bruce Benton, current chairperson of the Committee of Sponsoring Agencies (CSA) of the Onchocerciasis Control Programme in West Africa (OCP), to participate in the External Review of the Macrofil Chemotherapy Project.

The four persons who have agreed to make up the Macrofil External Review Group (MERG) are:

Dr Georges Jolles, ex-Research Director, Rhône-Poulenc Rorer;
Professor Dietrich W. Büttner, Head, Department of Parasitology, Bernhard-Nocht-Institut, Hamburg, Germany;
Dr Mervyn J. Turner, Senior Vice President, Basic Research, Merck Research Laboratory, USA;
Dr Akella Venkateswarlu, President, Dr. Reddy's Research Foundation, Hyderabad, India.

... Full coordinates for these persons are attached.

As chairperson of the MERG, Dr Jolles visited Geneva on Friday 31 January 1997, to confirm our arrangements for the External Review, and to select documentation to be sent out to you. Contrary to the invitation letter from Mr Benton, Dr Jolles anticipates that if you could spend three days at a first meeting and prepare a draft report, finalization of that report could be done by facsimile/email/air mail, etc. A second meeting would then only be held if there were specific problems in writing the report.

cc. Mr B. Benton, Chairperson, CSA
Professor D. Molyneux, Chairperson, EAC
Dr Tore Godal, Director, TDR
Dr K. Y. Dadzie, Director, OCP
Dr O. Christensen, Secretary CSA

WORLD HEALTH ORGANIZATION **ORGANISATION MONDIALE DE LA SANTE**

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In reply please refer to:
Prière de rappeler la référence: O80/181/1

Your reference:
Votre référence:

Dr Mervyn J. Turner
Senior Vice President
Basic Research
Mail Drop R80K
Merck Research Laboratory
Rahway, N.J. 07065-0900
USA

3 February 1997

Dear Dr Turner,

UNDP/FAO/WORLD BANK/WHO
Special Programme for
Research and Training in Tropical Diseases (TDR)
and the
Onchocerciasis Control Programme in West Africa (OCP)

We are pleased to refer to your conversations with Dr W.E. Gutteridge, Coordinator of Product Research and Development in TDR, concerning your possible participation in the forthcoming Phase IV External Evaluation of the OCP. As you may know, the objective of the OCP is "to eliminate onchocerciasis as a disease of public health importance and as an obstacle to socioeconomic development throughout the OCP area, and for the participating countries to maintain this achievement".

As the Programme will complete its six-year Phase IV operations by the end of 1997 and enter its final five year Phasing-out Period on 1 January 1998, it is proposed that an independent evaluation be carried out during 1997 in order to assess progress made until then in meeting the Programme's objective and in bringing OCP to a successful and lasting conclusion, as scheduled by 2002.

As part of the External Evaluation, an External Review Group will specifically review and evaluate the Macrofil Chemotherapy Project which is jointly financed and administered by TDR and OCP.

The overall objective of the Macrofil External Review Group (MERG) will be to assess the present research and development activities of Macrofil in the light of its objective to develop a macrofilaricide for use in public health programmes before OCP comes to an end

cc. Professor D. Molyneux, Chairperson, EAC
Dr Tore Godal, Director, TDR
Dr K. Y. Dadzie, Director, OCP

Dr Jolles has asked that the meeting be held in Geneva during the week of 17 - 21 March 1997, preferably from Tuesday 18 to Thursday 20 March. Would you please confirm at your earliest convenience, that you could attend a meeting on those dates.

In view of the closeness of the first meeting, I hope to send all documentation to you, by courier mail, before the end of this week.

Thank you for your agreement to participate in this review, and I look forward to receiving your reply regarding the date of the meeting.

With all good wishes.

Yours sincerely,

Dr C.D. Ginger
Manager
Macrofil Chemotherapy Project

in 2002, and to make proposals on a research strategy for the future with particular attention to its cost-effectiveness. We are pleased to invite you to be a member of this Macrofil External Review Group.

The Review of OCP, and of Macrofil, will be organized by the Committee of Sponsoring Agencies (CSA) of OCP and also of the African Programme for Onchocerciasis Control (APOC). The CSA, which consists of representatives of the United Nations Development Programme (UNDP), the Food and Agricultural Organization (FAO), the World Bank and the World Health Organization (WHO), monitors OCP and APOC operations.

I am enclosing for your information the two documents relating to the Phase IV External Evaluation [JPC 17.9(A)], and to the Review of Macrofil [JPC 17.9(B)] which were approved by the Joint Programme Committee (JPC) of OCP at its meeting in December, 1996.

Participation in this review would probably require up to two weeks of your time to read information on the Macrofil Project, and to travel to and take part in two meetings of the Macrofil External Review Group which will take place in Geneva in the first half of 1997. The MERG should complete its work by 31 May 1997, and its report will be submitted to the CSA, Directors, TDR, OCP and APOC, to the Expert Advisory Committee (EAC) of OCP in June 1997, to a Donors' Conference in October 1997, and finally presented to the JPC and APOC Joint Action Forum (JAF) in December 1997, for approval.

The OCP would be responsible for the costs of your travel on MERG business, and you would receive a daily allowance for expenses. While travelling for the MERG, you would serve as a WHO Temporary Adviser with the corresponding standards of travel and rates of per diem allowance.

We would be grateful if you would confirm to Dr Tore Godal, Director, TDR, your willingness to serve as a member of the Macrofil External Review Group, so that we can initiate the review.

We hope that you will agree to take part in this important undertaking and look forward to hearing from you.

Yours sincerely,

Bruce Benton

Mr B. Benton
World Bank
Chairperson, CSA

file

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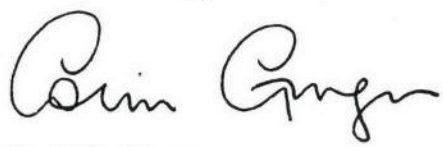

Dr C.D. Ginger
Manager
Macrofil Chemotherapy Project

WORLD HEALTH ORGANIZATION **ORGANISATION MONDIALE DE LA SANTE**

Téléphone Central/Exchange: 791. 21.11
Direct: 791 3802

In reply please refer to:
Prière de rappeler la référence: O80/181/1

Your reference:
Votre référence:

Dr Mervyn J. Turner
Senior Vice President
Basic Research
Mail Drop R80K
Merck Research Laboratory
Rahway, N.J. 07065-0900
USA

3 February 1997

Dear Dr Turner,

UNDP/FAO/WORLD BANK/WHO
Special Programme for
Research and Training in Tropical Diseases (TDR)
and the
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World Bank
Chairperson, CSA

file

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1) WHO-OCP
2) Macrofil Review

Téléphone Central/Exchange: 791. 21.11
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In reply please refer to:
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Your reference:
Votre référence:

Professor D.W. Büttner
Department of Parasitology
Bernhard-Nocht-Institutfur
Tropenmedizin
Bernhard-Nocht-Str. 74
D-20359, Hamburg

4 February 1997

Dear Professor Büttner,

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MEMBERS OF MACROFIL EXTERNAL REVIEW GROUP (MERG)

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Dr Mervyn J. Turner
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e-mail: gingerc@who.ch

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Hyderabad-500 016
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D Research
2 Macrofil Review

file copy Duke paper proper peer review system can't have individual proposing individual projects.

INVESTIGATION INTO THE MACROFILARICIDAL POTENTIAL OF IVERMECTIN AGAINST *ONCHOCERCA VOLVULUS*

(THE PROTOCOL, AND PROGRESS FROM JANUARY 1994 TO NOVEMBER 1995)

DETAILS OF RESEARCH PROJECT

1. Aims Of The Project.

The aim of this project is to investigate the macrofilaricidal potential of ivermectin against *Onchocerca volvulus*, when given at doses of 800 µg/kg (the highest dose approved in recent safety studies) annually for 3 years; to compare this with standard doses of 150 µg/kg annually (as originally recommended by the manufacturer, Merck and Co. Inc.) given for 3 years; and to compare these annual regimens with the effects of both dosage levels when given at intervals of 3 months over the same 3-year period.

Awaiting Ghana data due to 6 months time.

There is already some published evidence that repeated dosage with ivermectin has a degree of macrofilaricidal action against *O. volvulus*. If, by means of applied field research, a dosage regimen with this widely-used drug could be found that would kill or permanently sterilise the adult worms, this might serve to reduce markedly the duration and cost of the ivermectin distribution programmes (IDPs) that will be supported from 1997 onwards by the FAO/UNDP/WHO/World Bank African Programme for Onchocerciasis Control (APOC).

The continuing need to search for a macrofilaricide, effective against *O. volvulus* and suitable for large-scale use, has been emphasised by a number of potential donors to APOC. Most of the investigations on these lines has been entrusted to the OCP/TDR MACROFIL programme of the World Health Organization. Unfortunately, this body has paid little attention to the potential of ivermectin in this direction, and the project here described has so far been funded entirely by the River Blindness Foundation and executed by scientists from ORSTOM working in Cameroon.

2. Work Leading Up To The Project.

Ivermectin is a highly effective single-dose microfilaricide for *O. volvulus*, which produces minimal Mazzotti reactions and is suitable for large-scale use. After a single dose of 150 µg/kg, it also suppresses the production of microfilariae (mfs) by the female worms for a period of 3-12 months, and it may reduce the numbers of male worms available to fertilise the females. In communities where onchocerciasis is endemic, repeated annual treatments with ivermectin (at 150 µg/kg) on a large scale bring about a decrease in the load of *O. volvulus* mfs in the population and lead to a reduction, but not an interruption, of transmission of the parasite. Consequently, despite repeated annual treatments, persons living in endemic areas will continue to be (re-)infected; and the IDPs, now being established in most endemic countries, may therefore have to be sustained indefinitely. The duration of these expensive IDPs could be considerably reduced, with consequent economy in funding, if a new ivermectin regimen could be found which has either a macrofilaricidal action on *O. volvulus*, or which could effectively bring about a permanent sterilisation of the adult worms, particularly the females.

Unfortunately, despite many years of active research, no macrofilaricide suitable for large-scale treatment of onchocerciasis under rural conditions is presently available. However, there are a number of indications that ivermectin does have a variety of adverse effects upon the adult *O. volvulus* worms. Five studies (one in Liberia, three in Guatemala and one in Sierra Leone) have shown that ivermectin, when given at intervals of 2 weeks or of 3 or 6 months, may have some macrofilaricidal effect on this parasite (Duke *et al.*, (1991) *Bull. Wld. Hlth. Org.* **69**,

163-168; Duke *et al.* (1990), *Am. J. trop. Med. Hyg.*, **43**, *657-664*; Duke *et al.* (1991), *Am. J. trop. Med. Hyg.*, **45**, *132-137* ; Duke *et al.* (1992), *Am. J., trop. Med. Hyg.*, **46**, *189-194* ; Whitworth *et al.* (1992), *Trans. R. Soc. trop. Med Hyg.*, **86**, *277-280)*. Furthermore, when administered annually for 5 consecutive years at the conventional dose (150 µg/kg), not only did ivermectin suppress temporarily the production of mfs by the female worms but, following each treatment, a new stable level of microfilarial production was reached, which was 30% less than before that treatment {Plaisier *et al., J. Infect. Dis.* (1995), *in press}*. Whether this was due to the killing of a proportion of the adult females after each dose, or to a steady general loss of fecundity in all females, could not be ascertained . In addition, work by Professor Bruce Copeman (unpublished) on *O. gibsoni* in cattle has shown that a single high dose of ivermectin (5000 µg/kg) produces a 32% mortality among adult female worms of that species.

Until recently, the only parameter taken into account when evaluating the macrofilaricidal potential of ivermectin in humans has been the interval between treatments (varying from 2 weeks to 1 year), and the maximum dose recommended by the manufacturers (Merck and Co. Inc.) for onchocerciasis patients treated in mass campaigns has always been 150 µg/kg. However, early in 1993, on the basis of experience with doses of 400 µg/kg in the treatment of *Wuchereria bancrofti* {Cartel *et al.* (1992) *Trop. Med. Parasit.*, **43**, 263-266} and *Loa loa* {Martin-Prével *et al.*, (1993) *Amer. J. trop. Med. Hyg.*, **48**, *186-192* }, Merck & Co. Inc. agreed that doses of 400 µg/kg could be used experimentally in onchocerciasis patients in the present trial, provided that a pre-trial mf-clearing dose of 150 µg/kg was given 3 months before the first high-dose treatment. The purpose of this clearing dose was to avoid the possibility (at that time - January 1994 - still uninvestigated) that 400 µg/kg might produce very severe Mazzotti reactions in patients with onchocerciasis.

Since then, in September 1994, the results of a safety study on higher single doses of ivermectin, carried out by Dr K. Awadzi at the O.C.R.C., Hohoe, Ghana, have revealed no significant differences in the severity of the Mazzotti or other adverse reactions following the treatment of onchocerciasis patients with single doses of 150, 400, 600 or 800 µg/g ivermectin, whether given with or without a preceding clearing dose at 150 µg/kg (Awadzi *et al.*, (1995) *Trop. Med. Parasit.*, **46**, 131-137). As a result of these findings, Merck and Co. Inc. agreed that the high dose treatment in the present trial should be increased to 800 µg/kg, with effect from February 1995.

The choice of the 3-monthly treatments in the present trial, for comparison with the standard annual treatment, was based on the results of Duke *et al.*, (1990), *Trop. Med. Parasit.*, **42**, *175-180*, which produced evidence that the gestation period for mfs is about 3 months; and on the results of a small trial of 3-monthly dosage extending over three years in Guatemala (Duke *et al.* (1992), *Amer. J. trop. Med Hyg.*, **46**, *189-194*), which produced an excess mortality of 32.6% among female worms Three months is also an interval between treatments that could almost certainly be sustained over long periods in IDPs given by methods of community self-treatment, such as those being used currently in Mali, with encouraging results, by Dr Michel Pacqué of Sight Savers; and those under investigation and development by the TDR/AFR programme of WHO, using World Bank APOC funds. In addition, it is probable that 3-monthly dosage would be greatly appreciated by recipients of ivermectin since it is often their experience that, following a single dose of ivermectin, the itching skin lesions of onchocerciasis, although initially relieved within a few days, tend to recur after an interval of 3 months.

(NB ...)

3. Experimental Design And Methods Used In This Investigation

3.1. *General Outline of the Trial.*

The present project, executed by scientists from ORSTOM and from Cameroon, began in January 1994 using start-up funds from the River Blindness Foundation (RBF). The protocol has been planned to run for 4 years (January 1994 to December 1997), which covers 6 months of preparation, 3 years of treatment and 6 months of post-treatment assessment.

During 1994, 655 adult male African patients, infected with *O. volvulus* but otherwise in good health, were selected and allocated at random to 4 different treatment groups, each containing 163-164 subjects. From each patient, one group nodules was removed and quantitative skin-snip examinations performed before treatment began; and similar examinations will be repeated after 3 years of treatment, the nodules being removed 3 months after the last dose. The trial is being carried out under double-blind conditions; neither the examiners nor the patients receive any information concerning dose of the drug or the placebo which is given to the individual patients at each treatment round. As at November 1995, the trial has already been in progress for some 23 months. The first two rounds of definitive treatment were completed in August and November 1994 using a dose of 400 µg/kg for those patients on the high-dose regimens. Subsequent rounds of treatment, ~~using~~ 800 µg/kg for those on the high-dose regimens, have been carried out in February, May, August and November 1995 and will continue for a total of 3 years, as described below. The comparison between the various treatment groups will be based on the criteria of viability and reproductive capacity of the adult worms as evaluated by histological examination of nodules removed at the end of 1997.

This was started before safety data of invasi known

In the event that the nodules removed at the end of treatment reveal unmistakable evidence in any group of a significant degree of macrofilaricidal activity (30 % or more mortality than in the pre-treatment nodules or in the standard treatment "control" group), then all the patients will be offered continued treatment (by way of the Cameroon National IDP) with the most effective regimen revealed by the trial. If there is little or no evidence of macrofilaricidal action resulting from the higher or more frequent dosage regimens tested, but there is evidence of sterilisation of the adult worms, the patients in the group(s) so affected will be followed for an additional 12 months without further treatment and then submitted to a further nodulectomy to ascertain whether the worms have regained their reproductive activity or appear to be permanently sterilised. After this, and depending on the results obtained, these patients will continue to be treated, as most appropriate, either on the most effective regimen revealed by the trial, or on the presently accepted routine annual dosage at 150 µg/kg. If the trial reveals no evidence of macrofilaricidal or permanent sterilising action, then the patients will continue on the presently accepted annual dosage of 150µg/kg.

Throughout 1994 qnd 1995, the project has been funded entirely by the River Blindness Foundation by way of a generous personal donation from its Chairman, Mr John Moores. Financial support for the continuation of the present trial now being sought from the recently-launched FAO/UNDP/World Bank/WHO APOC programme in order to fund the running costs of this essential piece of applied field research over the 2-year period (1996 and 1997) until its conclusion. During this period, the River Blindness Foundation and ORSTOM will continue to fund all salaries under the terms of agreements already signed.

3. 2. *Description of the Trial Zone.*

The trial is being carried out in the Republic of Cameroon, in the northern parts of the contiguous Departments of Mbam and Inoubou and of Mbam and Kim, in the Central Province. This forest-savanna mosaic area is endemic for onchocerciasis and the ocular repercussions of

the disease are severe. A preliminary epidemiological survey undertaken in 30 villages located within 20 km of the River Mbam showed all of them to be hyperendemic (Boussinesq *et al.*, unpublished data). No previous ivermectin treatment, whether active large-scale or passive, had been given in the area of the present trial and no vector control operations have been undertaken, or are foreseen, therein. The villages (located between 10^0 55' and 11^0 30' E and 4^0 45' and 4^0 46' N) extend over an area of some 1'000 km^2, which includes a 40 km stretch of the River Mbam and a 20 km stretch of its major tributary the River Noun, each of which harbour very productive breeding sites of *Simulium* vectors. The overall population of the villages concerned is about 20'300 persons; and from 25 of these villages were drawn the 855 trial patients who answered to the trial inclusion criteria.

No firm predictions could be made as to the stability of the populations in the study villages over the proposed period of the trial but, from previous experience working in the area, it was expected that the drop-out rate would not be excessive and that the numbers remaining at the end of the trial would be sufficient to give provide a study with the necessary statistical power (see below). In fact, at the end of the 6th round of treatment (completed in November 1995), 802 patients (91.9%) remain in the trial; all the "drop-outs" have been for reasons unconnected with the drug regimen; and, in an independent examination carried out without "unblinding" the trial to those carrying out the research, it was revealed that the "drop-outs" were more or less evenly distributed among the four drug regimens.

3. 3. *Description of the Treatment Groups*

The four treatment regimens being evaluated are as follows.

Group 1: treatment at intervals of one year (total of 4 treatments) at a dose of 150 µg/kg p.a.; and at the intervening treatment rounds they receive placebo. (This group is tantamount to an ethically satisfactory "control" group which receives only the currently recommended ivermectin regimen. To have included an untreated control group was not considered to be ethically acceptable).

Group 2: treatment at intervals of 3 months (total of 12 treatments) at a dose of 150 µg/kg on each occasion.

Group 3: treatment at intervals of one year (total of 4 treatments), at a dose of 400 µg/kg on the first round, and subsequently at 800 µg/kg p.a. on the next 3 rounds; and at the intervening treatment rounds they receive placebo.

Group 4: treatment at intervals of 3 months (total of 12 treatments), at a dose of 400 µg/kg on the first two rounds of treatment, and at 800 µg/kg on eavh of the subsequent 10 rounds.

To minimise the possibility of severe Mazzotti reactions resulting from the first high dose (of 400 µg/kg), the subjects in all groups received a clearing dose of 150 µg/kg in May 1994, three months before those in groups 3 and 4 received their first 400 µg/kg dose. The purposes of this clearing dose, and the time interval of three months, were to eliminate safely most of the mfs from the skin and eyes before the first round of definitive high-dose treatment was given in August 1994. Since the trial patients had already been grouped in a blinded fashion, the clearing dose had to be administered to them all, regardless of the group to which they had been assigned.

3. 4. *Description of the Patients*

The patients selected to take part in the trial were males between 18 and 60 years of age, who had never received any filaricidal treatment, who had at least two nodules or groups of nodules, but who were otherwise in good health..

The purpose of the trial was explained to each patient, all of whom signed an "informed consent" agreement. An identification number was assigned to each subject before he was allocated at random to one of the four treatment groups. A Polaroid photo of each patient was taken at the beginning of the trial in order to ensure subsequent correct identification.

Merck and Co. Inc. have kindly agreed to supply both the Ivermectin (Mectizan^{R}) and the placebo doses for all trial patients in the form of gellules, which are indistinguishable except under code. The only person in Cameroon to be aware of the code is the project's pharmacist in Yaoundé who, before each treatment round, prepares the doses that should be given to each patient. Each patient's dose is put in a separate sachet containing his individual card, identification number and photograph. Any adverse reactions to treatment are recorded and treated by mobile teams which remain in the area for 72 hours after each treatment. Any patients with severe adverse reactions (there has been none so far) will be transported to the "Hôpital Départemental" in Bafia or to the Central Hospital in Yaoundé, 150 km from the study site.

Ethical clearance for the trial was obtained from the necessary authorities in the Cameroon Ministry of Health, Merck & Co. Inc., and ORSTOM.

3. 5. *Randomisation of Groups*

After stratification on the basis of (*a*) age 18-29 yrs; 30-44 yrs; and 45-60 yrs), (*b*) no. of nodules (2; and >2); and (*c*) endemicity level of the village (CMFL 10-40, 41-60, 61-70, and 71-114 mfs/snip); each of the 655 patients was allocated at random to one of the four treatment groups described in section 3.3 above.

3. 6. *Methodology and Evaluation Criteria*

3. 6. 1. *Pre-Treatment Examinations*

(a) Numbers and distribution of nodules and examination of their contained worms. At the outset of the trial, the patients were stripped to their loin cloths and, after careful examination in good light by a physician, the distribution and size of each man's nodules were marked on a body chart. Subsequently, all patients are being re-examined in a similar manner once a year before each anniversary of the first round of treatment. Any new nodule is marked on the chart along with the date of its discovery; and any nodule which has disappeared is similarly recorded.

Before treatment began, one nodule or one group of nodules (chosen at random) was removed surgically from each patient. The nodulectomies were performed, under sterile conditions in a Health Centre, by a physician or a nurse specialised in surgery, using local anaesthesia (2% lignocaine). Each nodule was fixed in a separate plastic bottle containing a 20-fold excess volume of fixative (70% ethanol, 10% glycerol, 20% water) and bearing the patient's identification number and the date of nodulectomy. 24 hrs later the nodules were placed in fresh fixative and stored therein.

Assessment of the viability and reproductive activity of the adult worms will be done by routine histology, after embedding in paraffin wax, cutting sections at 6 μm, and staining with haematoxylin and eosin. The histological preparation is done in the "Service d'Anatomie Pathologique et de Cytologie" of the Centre Pasteur du Cameroun (Yaoundé). One nodule from each patient, removed before treatment began, has been cut and stained. Apart from making sure that the slides have been prepared satisfactorily, no detailed histological examination has yet been made. In order to avoid bias on the part of the examiners, it has been decided that the examination should be deferred until the nodules removed at the end of treatment can be examined, along with the pre-treatment nodules, in a "blinded" manner. An excess of uncut nodules removed pre-treatment remains from 342 patients who are still taking part in the trial. These have been stored in the fixative for subsequent examination, as may become necessary, to confirm or amplify the results, either by further histology or by collagenase digestion. Any excess of post-treatment nodules will be treated similarly.

(b) *Microfilarial concentrations in the skin.* A parasitological examination of each patient was made before treatment. A skin snip was taken from each iliac crest, using a 2 mm Holth corneo-scleral punch. Each snip was placed immediately in a separate well of a microtitre plate containing 300 μl of normal saline. After 24 hrs, the emerged *O. volvulus* microfilariae were counted under a low-power microscope. The snips were then fixed in a mixture of 70% ethanol, 10% glycerol and 20% water for later digestion in collagenase in order to count the microfilariae which remained in them. Before digestion they were blotted dry and weighed. The sum of the two counts from each snip gives the total count of mfs, which is then expressed as mfs/mg of skin. The punches are sterilised by flaming for 10 seconds, then during 1 minute in sodium hypochlorite, followed by one minute in ethanol. They are then rinsed in water and dried before they are next used. A thick blood smear (30 μl) is also made and, after staining with Giemsa, the mfs of *Loa loa* and *Mansonella perstans* therein are counted.

3. 6. 2.. *Evaluation of the Effect of Ivermectin on Adult Worms and on Microfilarial Loads In the Skin*

(a) Adult worms. This assessment of the effects of the different ivermectin regimens on the adult worms will be done by "blinded" histological examination of the nodules, having regard to the viability of both male and female worms, to the embryogenic performance of the females, and to the relative numbers and spermatogenic performance of the males. The post-treatment nodules will be removed 3 years after the first dose of ivermectin and 3 months after the last dose. The worms from nodules in each treatment group will be compared in all the above respects with those in the other treatment groups and also with the worms removed before treatment began. Records will be kept of all nodules which disappear during the course of treatment. Any new nodules which first appear after treatment began will be removed during the final nodulectomy round and labelled as such for examination. In order to assess possible natural changes that may have occurred in the worm populations of untreated persons living in the villages from which the patients were drawn, a sample of up to 100 nodules will, if possible, be removed at the end of the study from a like number of untreated persons who have been living in the treated communities over the period of the trial.

The microscopic examinations of nodules will be done independently and in a blinded fashion by Drs B.O.L. Duke, M. Santiago, and M. Boussinesq. The sectioned worms will be classified as described by Büttner *et al., (Trop. Med. Parasit., 39: 390-417* (1988); Striebel, H. *(Trop. Med. Parasit.,* 39, *387-389* (1988); and Duke *et al., (Trop. Med. Parasit.,* 41; *387-402,* (1990) - see Annex 2.. The examination of all nodules removed before treatment and those removed at the end of treatment will be examined together in a blinded manner, during the last quarter of 1997 and early in 1998, so as to prevent any bias that might result from the knowledge of whether they contained pre- or post-treatment worms. The histopathologists will not receive

any information as to the origin of the individual nodules they examine until the code is broken after they have reported. In the event that independent confirmation of positive results obtained by the 3 examiners is required for any reason, then a set of coded slides will be referred to an independent well-qualified examiner (possibly Professor D. W. Büttner or Dr H. P. Striebel) for examination on a contract basis.

As at November 1995, from the 602 patients still taking part in the trial, we hold alcohol-fixed pre-treatment reserve nodules from 340 of them; and it is likely that a similar number of "spare" nodules will be obtained at the post-treatment nodulectomies in 1997. In the event that histological examination of further stored nodules from the pre-treatment or post-treatment nodulectomies is considered necessary to confirm a positive result of the trial, then the remaining available nodules will be sectioned and examined histologically. Alternatively, in the event that examination of collagenase-digested worms is considered desirable to confirm or supplement the results of histolological examination, the remaining available coded nodules stored in the alcoholic fixative will be referred to a suitable, skilled examiner, on a contract basis for examination by the methods of Schulz-Key (1988) *Trop. Med. Parasitol*, **39**, 423-440 and/or that of Duke (1990) *Trop. Med. Parasitol*, **41**, 25-28. Any of these putative supplementary examinations would demand additional supplementary funding after the end of the field project in 1997.

(b) Microfilarial Concentrations in the Skin. The counts of mfs in the skin of each patient at each examination will be made under "blinded" conditions and a comparison of the effects of the four regimens on mfs loads will be made only after the code has been broken. The method employed gives the most accurate assessment of the total numbers of mfs in a skin snip.

3. 7. *Calculation of the Numbers of Persons Needed and of the Power of the Study.*

The main criterion by which the outcome of the trial will be assessed is the proportion of adult male and female *O. volvulus* which are found dead in the nodules removed after three years of treatment (late 1997). This proportion will be estimated by histopathological assessment, supplemented, if necessary, by a study of worms from collagenase-digested nodules.

Not knowing the variance in the above criteria that may follow treatment, and in order to err on the safe side, we chose at the outset to overestimate the number the number of subjects to be included in the study.

The significant level of macrofilaricidal action for this study has been taken as an excess adult worm mortality rate of 30% or more above that found in the pre-treatment nodules or in the "control" group receiving 150 µg/g annually. This figure was chosen on the basis of the results obtained by Duke (1992) *Amer. J. trop. Med. Hyg.*, **46**, 189 - 194). We also know that, in any normal sample of untreated nodules, some 10% of the adult worms will be dead.

In order to detect a significant increase in mortality we have had recourse to a unilateral test in which:-

the *alpha* risk of the first order is 2.5%; and the *beta* risk of the second order is 2.5% ; giving the study a power of 97.5%.

In these conditions the following formula can be applied:

$$N = \frac{(\varepsilon_{2\alpha} + \varepsilon_{2\beta})^2}{2(\arcsin Pb - \arcsin Pa)^2} \quad \text{(Facultative)}$$

where Pa is the proportion of worms found dead in the reference group, and Pb is the proportion found dead in the group under comparison.

This calculation gives the number of subjects needed in each group as 58 or a total of 232 subjects for the four groups.

We estimated that the proportion of drop-outs (from natural death or emigration) during the first 3 years of treatment would be of the order of the order of 20%, which demanded the recruitment of a minimum of 300 persons into the trial at the outset. However, we wished in addition to make provision for a possible assessment of macrofilaricidal action based on collagenase-digested nodules as well as on nodule histopathology. At the initial round of nodulectomies, 58% of operations provided more than one nodule and would thus permit of making an assessment in both ways. We hypothesised that at the second round of nodulectomies at the end of 1997, a like proportion of patients would provide more than one nodule at each operation site. Thus, in order to be sure of having 300 patients with more than one nodule at the same operation site, it was necessary to include 500 persons in the trial. The uncertainties about the level of natural "drop-outs " in the cohort, as well as about the variance of accessory criteria, led us to err on the safe side and include 655 in the study.

3. 8. *Data Analysis*

All data obtained will be recorded and analysed by computer. The results concerning adult worms will be analysed as by Duke *et al., (Amer. J. trop. Med. Hyg.*, 46: *189-194* (1992)).

The data will also be made available for subsequent analysis by the ONCHOSIM programme (Plaisier *et al., Computer Methods and Programmes in Biomedicine*, 31: *43-56* (1990)), and by the SIMON programme (Davies J.B. *Ann. trop. Med. Parasit., 87: 412-63, (*1993)), so that any effects of ivermectin on the adult worms may be integrated with these models.

3. 9. *Treatment of Other Eligible Persons Living in the Villages from which the Trial Patients are Drawn and Assessment of the Impact of Ivermectin on the Amount of Transmission of* O. Volvulus *to which those Communities are Subjected.*

To ensure the co-operation of the communities from which the trial patients were drawn, and to satisfy ethical requirements, all other people who live in those communities and who are eligible to receive ivermectin, are being offered treatment annually at a dose of 150 µg/kg. Palliative treatment for any side effects of treatment is provided over the first 72 hours after treatment and as necessary.

The ivermectin treatment of the trial patients and the other eligible villagers may reduce the amount of transmission in the study area, and hence the amount of transmission to which the trial patients are exposed after the beginning of the trial. The possible effects of this will have to be taken into account when analysing the data on the viability of the adult worms in nodules removed from the patients at the end of trial. The effect of ivermectin treatment on the amount of *O. volvulus* transmission in these communities is being assessed by examination of two quantitative skin snips taken from each 5-year-old child which has reached a weight of 15 kg or a

height of 95 cm over the year before receiving its first annual dose of ivermectin. It is estimated that these children will form 2-3% of the population and that consequently there will be a pool of 400-600 children available to be snipped each year. Data on the prevalence and intensity of infection in their age-group will be analysed, as was done by Taylor *et al.*, (1990), *Science*, **250**, *116-118*, in order to obtain an estimate of any change in the annual incidence of infection and thus of any reduction in transmission that may have taken place during the trial.

3. 10. *Study Schedule*

In January and February 1994 the trial patients were selected; the first mass treatment of all eligible persons in the villages was carried out; and the 5-year-old children were skin snipped. The mass treatment of all eligible villagers and the snipping of 5-year-olds was repeated in January/February 1995 and will be repeated each year until the end of the project. In March and April 1994, the pre-treatment detailed examinations, skin snipping and nodulectomies of the trial patients were carried out, and in May 1994 the clearing dose of 150 µg/kg was given to the patients in all groups. In August 1994, the first definitive treatment of patients in all four groups was completed, followed by the second round in November 1994 (both rounds using a maximum "high" dose of 400 µg/kg, where applicable). The 4th, 5th, 6th and 7th rounds of ivermectin or placebo (using a maximum "high" dose of 800 µg/kg, where applicable) were given in February, May, August and November, 1995.

The past and proposed future schedule of treatments and nodulectomies is shown in tabular form in Annex I.

Histological examination of the effects of treatment on the adult worms will be completed during the last quarter of 1997 or by early 1998; and a decision will then be made, based on the results obtained at that time, as to how to proceed with the further treatment of the trial patients, and as to what further examinations of the nodules already excised may be necessary.

Currently it is felt that the patients should be offered continuation of treatment on whichever regimen has achieved the best results in killing or sterilising the adult worms. A possible modification of their further treatment might be required if the 3-year nodules from any group reveal an apparent sterilisation of the adult worms without their being killed. In these circumstances it might be desirable to stop further treatment of the remaining patients in any group where this situation pertains, and to follow them with a further nodulectomy 12 months after their last dose of ivermectin. This would enable us to assess whether any of the apparently sterilised worms are capable of recovering their reproductive potential and, if so, how quickly this recovery takes place. Such a further investigation would involve a supplementary project and a separate budget.

SUMMARY OF PROPOSED RESEARCH

The control of onchocerciasis currently depends mainly on ivermectin (an effective, innocuous, single-dose microfilaricide and microfilarial suppressant for *Onchocerca volvulus)* distributed on a large scale. However, at approved dosage (150 µg/kg annually) and with the usual 60-70% coverage obtained, it may reduce, but does not interrupt transmission. Therefore costly ivermectin distribution programmes (IDPs), including those funded by the FAO/UNDP/WHO/World Bank African Programme for Onchocerciasis Control (APOC), may have to be sustained indefinitely until and unless a macrofilaricide for *O. volvulus*, suitable for large-scale use, is discovered.

Impossible to distinguish by current methods

Since 1990, evidence has accumulated suggesting that ivermectin given over long periods or at intervals of less than one year, may have a macrofilaricidal or permanent sterilising action on a proportion of adult *O. volvulus*. Furthermore, the recent good results of safety studies in onchocerciasis patients have cleared the way for investigations into the macrofilaricidal potential of this drug when used at doses up to 800 µg/kg.

The present trial began in January 1994, funded by the River Blindness Foundation (RBF) and executed by ORSTOM. It is taking place in the Republic of Cameroon on 655 male volunteers, aged 18 - 60, infected with *O. volvulus* but otherwise in good health, and coming from 25 hyperendemic villages near the River Mbam. It will last for 4 years (until the end of 1997). All treatments and examinations are done double-blind. After stratification for age, number of nodules and village CMFL, the patients have been divided into four equal groups receiving ivermectin at (*a*) 150 µg/kg annually (ethically acceptable "controls") to a total of 4 doses, (*b*) 150 µg/kg 3-monthly to a total of 12 doses, (*c*) 800 µg/kg annually to a total of 4 doses and (*d*) 800 µg/kg 3-monthly to a total of 12 doses. The histology of the adult worms in excised nodules (assessing their viability and reproductive potential), and the mean microfilarial counts in skin snips from the patients in each group 3 months after the conclusion of 3 years treatment, will be compared between treatment groups and with those taken before treatment. If, at that time, there is evidence of an excess mortality of ≥30% in the adult worms from any of the treatment groups (as compared with those in the pre-treatment nodules or in the "control" group receiving the standard annual dose of ivermectin), then, with certain provisos defined in the text, all patients will be offered continued treatment on the most effective regimen.

All other persons living in the 25 villages from which the trial patients come, who are eligible to take ivermectin, are offered standard annual ivermectin treatment; and skin snips are being taken each year from 5-year-old children before their first round of treatment, to assess the effect of the campaign on local transmission.

The World Bank, now that its APOC fund has been launched in December 1995, is requested to consider funding the remainder of the running costs (estimated at $ 188'400 for 1996 and 1997) of this potentially important operational research project, while the River Blindness Foundation and ORSTOM will continue to fund the salaries of the executing personnel (estimated at $ 110'000).

ANNEX 1

PROPOSED IVERMECTIN TREATMENT SCHEDULE

	ANNUAL TREATMENT		3-MONTHLY TREATMENT	
	GROUP 1	GROUP 3	GROUP 2	GROUP 4
MAR/APR '94	Pre-treatment	nodulectomy	and skin	snipping
MAY '94	150	150	150	150
AUGUST '94	150	400	150	400
NOVEMBER '94	Placebo	Placebo	150	400
FEBRUARY '95	"	"	150	800
MAY '95	"	"	150	800
AUGUST '95	150	800	150	800
NOVEMBER '95	Placebo	Placebo	150	800
FEBRUARY '96	"	"	150	800
MAY '96	"	"	150	800
AUGUST '96	150	800	150	800
NOVEMBER '96	Placebo	Placebo	150	800
FEBRUARY '97	"	"	150	800
MAY '97	"	"	150	800
AUGUST '97	150	800	Nodulectomy & Placebo	Skin snipping Placebo
NOVEMBER '97	Nodulectomy &	Skin snipping		

N.B. All ivermectin doses are given as µg/kg.

ANNEX 2.

ADULT WORM CLASSIFICATION - DEFINITIONS

1. FEMALE WORMS

CATEGORY

F		Fecund worms, inseminated or re-inseminated, producing oocytes and embryos of all stages up to microfilariae.
	FF	Worms in full production of oocytes and embryos (probably younger worms).
	FO	Worms with less than full production of oocytes and embryos (probably older worms).
S		Potentially fertile worms, not currently inseminated, shedding oocytes which are transforming into unfertilised ova and then degenerating.
	SF	Worms in full production of oocytes (probably younger worms).
	SO	Worms producing reduced numbers of oocytes (probably older worms)
I		Intermediate worms changing from Category F to S or *vice-versa*
	IA	Recently (re-)inseminated worms changing from Category S to F, with a predominance of pre-microfilarial stages.
	IZ	Worms changing from Category F to S with microfilariae and brezels in the anterior uteri and with degenerating ova behind them.
E		Empty senescent worms, no longer producing oocytes, with empty uteri or no uteri.
M		Moribund worms (alias "probably dead"), with several sections appearing dead (as in D below) and others where the worm appears still alive but looks poorly and unlikely to recover.
D		Dead worms (degenerate; collapsed; calcified; with giant cells invading; and sometimes full of basophilic cellular material).

This classification is based on the system adopted by Duke, Zea-Flores and Gannon (*Trop. Med. Parasit.*, (1990), 41, 387-402)

2. MALE WORMS

Male worms are recorded as being alive, moribund or dead.

Those alive are recorded as having normal or abnormal spermatogenesis

NOTES

1. Where degenerate or relict embryos are seen in female worms, these are recorded as:

   Dev = sundry developing embryos, short of mfs
   Mor = morulae
   Gst = gastrulae
   Brz = brezels
   Mfs = microfilariae

2. Where a female worm is classed as moribund or dead, but it is still possible to make out what its classification would have been when in life, then its former classification is shown in brackets, e.g. (SO), (SF), (E), (FO), (FF) etc.

3. It is not always easy to be sure how many female or male worms there are in any given nodule, especially when the coils of different worms become intermingled. It is often helpful to examine the slide first with a magnifying glass or at very low power on the microscope. This may enable one to see where the separate worms are coiled.

4. It is important to know which nodules were calcified and could not be sectioned for this reason; also which nodules needed decalcification before they could be sectioned. Calcification usually means that the contained worms, or at least some of them, are dead.

5. In female worms that have been subjected to ivermectin (or treatment with other drugs) it is important to record exactly which embryogenic forms are present and whether any of them are degenerate; and which embryogenic forms are absent.

6. For male worms following ivermectin, it is important to make sure, as far as possible, how many there are in each nodule; and to determine whether their spermatogenesis appears normal.

7. The relics of dead male worms (which are small in size) disappear or become unrecognisable more quickly than the relics of female worms

8. The presence of apparently live microfilariae in the capsule of a nodule indicates that at least one female worm in the nodule must be fecund.

SUMMARY TABLE

		NUMBER	Percent
A.	Total no. nodules		
B.	Total no. female worms		
C.	Total no. female worms alive	C/B	
D.	" " " " " & producing embryos	D/C	
E.	" " " " " , producing embryos and with degenerating embryos	E/D	
F.	Total no. female worms alive but out of embryonic production	F/C	
G.	" " " " " " " " " " and yet containing relict embryos	G/F	
H.	Total no. female worms moribund	H/B	
I.	" " " " dead	I/B	
J.	Total no. male worms seen		
K.	" " " " alive	K/J	
L.	" " " " moribund	L/J	
M.	" " " " dead	M/J	
N.	" " " " with normal spermatogenesis	N/J	
O.	" " " " " abnormal "	O/J	
P.	Total no. nodules with no male seen	P/A	
Q	Total nodules with mfs in capsule	Q/A	
R.	" " " " " " but no male seen	R/A	
S.	Ratio of males : females (all worms)	J/B	
T.	" " " : " (live ")	K/C	
U.	Mean no. of males nodule	J/A	
V	" " of females "	B/A	

BUDGET FOR CAMEROON MACROFILARICIDE PROJECT - 1996/1997

RUNNING COSTS

ITEM	1996	1997
A. 1. MATERIALS AND CONSUMABLES		
FUEL/LUBRICANTS	7'300	10'300
MAINTENANCE OF VEHICLES	9'000	12'500
PROVISION FOR HEAVY REPAIRS TO VEHICLES AT END OF THEIR LIVES	NIL	10'000
DRUGS FOR SIDE EFFECTS	2'300	2'600
SURGICAL MATERIALS	NIL	8'000
COLLAGENASE	NIL	800
GLASS/PLASTIC WARE	800	800
OFFICE STATIONERY	1'900	2'400
REAGENTS	650	650
SUB-TOTAL	21'950	48'050
A. 2. MISCELLANEOUS		
RENTING PREMISES	4'900	4'900
PER DIEM (LOCAL)	21'000	27'000
DATA ANALYSIS, COMPUTER ENTRY & PROCESSING	10'500	13'000
PROCESSING AND EXAMINING NODULES	NIL	16'200
TRAVEL (SUPERVISOR AND DATA PROCESSOR) BY AIR	4'100	4'100
TRAVEL (SUPERVISOR) PER DIEM	2'450	2'450
PHONE, FAX, POST	2'500	5'300
SUB-TOTAL	45'450	72'950
TOTAL FONCTIONNEMENT	67'400	121'000

GRAND TOTAL FONCTIONNEMENT FOR 1996-97 = $188'400

Would consider high, but not unreasonable.

- Contingency request of $34,000

JUSTIFICATION FOR FINANCIAL SUPPORT REQUESTED

The River Blindness Foundation has already contributed $ 255'000 to puchase all vehicles and equipment and run the project for the first two years (1/1/94 through 31/12/95), and has ensured the salary of Dr Jacques GARDON from 1/7/95 through 31/12/96. In conjunction with ORSTOM it will also continue to fund his salary, fringe benefits, and annual leave air passage through 1996 and 1997 at a further estimated cost of $110'000.

ORSTOM and the French Ministry of Co-operation and Development have funded the salaries of Dr Michel BOUSSINESQ and Dr M. SANTIAGO respectively through 1994 and 1995 and will continue to fund them through 1996 and 1997.

The salaries of other personnel involved in the trial (physicians, technicians in Public Health, nurses, assistants, secretaries and drivers) are assured by the Cameroonian Ministry of Health.

Staff employed on the project

The scientists involved in the project are the following:-

Dr M. BOUSSINESQ (salary assured by ORSTOM). His role as Principal Investigator is to co-ordinate the project in Yaoundé and in the field, take part in the nodulectomy programme and to examine the sections of the nodules;

Dr. Jacques GARDON (salary assured by RBF). His role is to ensure the treatment and follow-up of all trial patients; to carry out treatment of all villagers annually; to conduct nodulectomies and skin snip examinations; and maintain and analyse all records.

Dr. M. SANTIAGO (salary assured by "Ministère Francaise de la Coopération"). He is responsible for processing all nodules and examining the sections.

Dr. Natalie GARDON (part-time, piece work). Responsible for data entry and analysis.

Dr Brian O. L. DUKE (no salary) General planning and supervision. Examination of nodules.

Running Costs requested

The planned budget for running costs in 1996 and 1997 have been based on the expenses incurred during 1994 and 1995. Three types of operation in the field can be distinguished: (1) treatment of trial patients only; (2) treatment of trial patients and of the other people in the villages; and (3) treatment and nodulectomies of trial patients. In 1996 there will be three operations of Type 1 and one of Type 2; in 1997 there will be two operations of Type 1, one of Type 2 and one of Type 3.

Our estimates, based on experience of numbers of persons treated in 1995, on kilometrage covered and numbers of vehicles used, and on local per diem rates, give the following figures for each type of operation:

	Type 1	Type 2	Type 3
Drugs for side effects	300	1400	600
Fuel and lubricants	1500	2800	4500
Maintenance of vehicles	2000	3000	5500
Per diem	5000	6000	11000

The amount spent on fuel and lubricants covers four 4WD vehicles used in the programme. The study area is over 1000 km^2 and some 20'000km are covered each year. Repairs and maintenance of vehicles is calculated at about 1.2 x the cost of fuel.

The per diem rates in Cameroon are as follows: MD 20'000CFA = $40; nurses 15'000 CFA = $30; Public Health Technicians 13'000CFA = $26; Assistants, secretaries and drivers 6'000CFA = $12; Interpreters 2'000CFA = $4. Operations of Type 1 last about 3 weeks and the personnel includes 3 MD, 1 TPH, 4 drivers and 2 secretaries. Operations of Type 2 last about 3 weeks and involve 4 MD, 1 TPH, 4 drivers, 4 secretaries, and 1 assistant. Operations of Type 3 last for at least a month and involve 4 MD, 1 TPH, 4 nurse, and 4 drivers.

A house is rented in Bafia for use as a laboratory and a store. The rent, including water, electricity and caretaking, is $4'900 p.a.

Processing of nodules (embedding sectioning, staining and examination) is estimated at $25 per nodule. About 650 nodules will have to removed in 1997.

Dr BOUSSINESQ will be posted to France early in 1996 but he will return to Cameroon for about 2 months each year to supervise the operations of Types 2 and 3. This accounts for his travel by air and his per diem.

Data entry and analysis and computer processing will be done on a part-time basis by Dr Natalie GARDON.

Fax, phone and postal charges are based on past experience of the project.

REFERENCES (Research Project)

Büttner, D.W., Albiez, E.J., von Essen, J. & Erichsen, J. (1988). Histological examination of adult *Onchocerca volvulus* and comparison with the collagenase technique. *Trop. Med. Parasit.*, **39**: 390-417.

Cartel, J.L., Moulia-Pelat, J.P., Glaziou, P., Nguyen, L.N., Chanteau, S. & Roux, J.-F. (1992). Results of a safety trial on single-dose treatments with 400 µg/kg of ivermectin in bancroftian filariasis. *Trop. Med. Parasitol.*, **43**: 263-266.

Davies J.B. (1993). Description of a computer model of forest onchocerciasis transmission and its application to field scenarios of vector control and chemotherapy. *Ann. Trop. Med. Parasit.*, **87**: 41-63.

Duke, B.O.L., Pacqué, M.C., Muñoz, B., Greene, B.M. & Taylor, H.R. (1991). Viability of adult *Onchocerca volvulus* after six 2-weekly doses of ivermectin. *Bull. Wld Hlth Org.*, **69**: 163-168.

Duke, B.O.L., Zea-Flores, G., Castro, J., Cupp, E.W. & Muñoz, B. (1990). Effects of multiple monthly doses of ivermectin on adult *Onchocerca volvulus*. *Am. J. Trop. Med. Hyg.*, **43**: 657-664.

Duke, B.O.L., Zea-Flores, G., Castro, J., Cupp, E.W. & Muñoz, B. (1991). Comparison of the effects of a single dose and of four six-monthly doses of ivermectin on adult *Onchocerca volvulus*. *Am. J. Trop. Med. Hyg.*, **45**: 132-137.

Duke, B.O.L., Zea-Flores, G., Castro, J., Cupp, E.W. & Muñoz, B. (1992). Effects of three-month doses of ivermectin on adult *Onchocerca volvulus*. *Am. J. Trop. Med. Hyg.*, **46**: 189-194.

Duke, B.O.L., Zea-Flores, G. & Gannon, R.T. (1990). On the reproductive activity of the female *Onchocerca volvulus*. *Trop. Med. Parasitol.*, **41**: 387-402.

Duke, B.O.L., Zea-Flores, G. & Muñoz, B. (1991). The embryogenesis of *Onchocerca volvulus* over the first year after a single dose of ivermectin. *Trop. Med. Parasitol.*, **42**: 175-180.

Martin-Prével, Y., Cosnefroy, J.-Y., Tshipamba, P., Ngari, P., Chodakewitz, J.A. & Pinder, M. (1993). Tolerance and efficacy of single high-dose ivermectin for the treatment of loiasis. *Am. J. Trop. Med. Hyg.*, **48**: 186-192.

Plaisier, A.P., van Oortmarssen, G.J., Habbema, J.D.F., Remme, J. & Alley, E.S. (1990). ONCHOSIM: a model and computer simulation program for the transmission and control of onchocerciasis. *Computer Methods and Programs in Biomedicine*, **31**: 43-56.

Striebel, H.P. (1988). Proposed form to evaluate some histological aspects of macrofilarial morphology, its age dependent alterations and drug related changes in nodules of *Onchocerca volvulus* and *O. gibsoni*. *Trop. Med. Parasit.*, **39**: 367-389.

Taylor, H.R., Pacqué, M., Muñoz, B. & Greene, B.M. (1990). Impact of mass treatment of onchocerciasis with ivermectin on the transmission of infection. *Science*, **250**: 116-118.

Whitworth, J.A.G., Morgan, D., Maude, G.H., Luty, A.J.F. & Taylor D.W. (1992). A community trial of ivermectin for onchocerciasis in Sierra Leone: clinical and parasitological responses to four doses given at six-monthly intervals. *Trans. R. Soc. Trop. Med Hyg.*, **86**: 277-280.

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COLLABORATION ON A GRANT

Collaborators, i.e. scientific/medical colleagues who are associated with a research proposal and named in the body of the application, but are not co-applicants, are asked to complete this form.

Name of Grant Applicant: Dr. Michel BOUSSINESQ

Department and Institution: Centre Pasteur du Cameroun

B.P. 1274 YAOUNDE CAMEROON

Name of Collaborator: Dr. B.O.L. DUKE

Full Address: 2 Hillside

LANCASTER LAI IYH

U.K.

Title of Research Project: Investigation of the macrofilaricidal potential of ivermectin at high and frequent doses against *Onchocerca volvulus* in Cameroon.

Extent and nature of collaboration: Reading histological slides of nodules ; advice on design and management of project.

I confirm that I am willing to collaborate as stated above with: Dr. M. BOUSSINESQ *et al.*

..... on this research project

Signed: [signature] Date: 2 January 1995

(if more than one copy of this form is required, please photocopy as necessary)

MINISTRY OF PULIC HEALTH

REPUBLIC OF CAMEROON
Peace-Work-Fatherland

ETHICAL CLEARANCE FORM

TITLE OF THE PROJECT:

INVESTIGATION OF THE MACROFILARICIDAL POTENTIAL OF IVERMECTIN AGAINST ONCHOCERCA VOLVULUS IN CAMEROON.

PRINCIPAL INVESTIGATOR:

Dr Michel BOUSSINESQ, ORSTOM/CENTRE PASTEUR, YAOUNDE CAMEROON

STATEMENT:

THE ABOVE MENTIONED RESEARCH PROJECT HAS BEEN EXAMINED; NO OBJECTIONS WERE FOUND ON ETHICAL GROUNDS BY THE MINISTRY OF PUBLIC HEALTH OF CAMEROON.

YAOUNDE, the 19 AOUT 1993

Pr. Joseph MBEDI

MINISTERE DE LA SANTE PUBLIQUE
MINISTRY OF PUBLIC HEALTH

REPUBLIQUE DU CAMEROUN
Paix — Travail — Patrie

REPUBLIC OF CAMEROON
Peace — Work — Fatherland

N° D31 /L/MSP/SG/DMPR/DAMPR/SDE/SLE

Yaoundé, le 21 NOV. 1994 19
the

Réf. :
Ref.

Le Ministre de la Santé Publique
The Minister of Public Health

Objet : Modification du Protocole d'évaluation des potentialités macrofilaricides de l'ivermectine contre Onchocerca valvulus.
Subject

à M ONSIEUR LE DOCTEUR Michel BOUSSINESQ
to ORSTOM / CENTRE PASTEUR - YAOUNDE -

Monsieur le Docteur,

Comme suite à votre lettre du 26.9.1994 relative à l'objet repris en marge,

J'ai l'honneur de vous donner mon accord de principe pour l'augmentation des doses de Mectizan chez les patients ayant déjà reçu deux traitements par ce médicament.

A cause des effets neurologiques probables du Mectizan chez les malades présentant une double infection onchocercose-loase, il serait souhaitable d'exclure de votre échantillon tous les malades souffrant de la loase.

Vous voudrez enfin faire un monitoring intense des malades qui seront traités avec les fortes doses de Mectizan et me tenir régulièrement informé de l'évolution de votre enquête.

Je vous prie de croire, Docteur, à l'expression de ma parfaite considération.-

Joseph OWONA

Kenneth R. Brown, M.D.
Executive Director
Worldwide Regulatory Liaison
Biologics/Vaccines

Merck & Co., Inc.
West Point PA 19486-0004
Fax 610 397 2962
Tel 610 397 2552
215 652 5000

August 9, 1994

MERCK
Research Laboratories

Dr. Colin Ginger
WHO
1211 Geneva 27
Switzerland

FAX 011-41-22-791-0746

Dr. Brian Duke
River Blindness Foundation
#2 Hillside, Lancaster LA1 1YH
United Kingdom

FAX 011-44-524-388-942

Dear Dr. Duke and Dr. Ginger:

Thank you for sending a copy of Dr. Awadzi's report on the safety study of high doses (600 mcg/kg and 800 mcg/kg) of ivermectin (MECTIZAN®) in onchocerciasis. The results are most encouraging. Accordingly, we have no objection to Dr. Boussinesq increasing the top dose in his present study of the macrofilarioidal potential of ivermectin against *Onchocerca volvulus* in Cameroon from 400 mcg/kg to 800 mcg/kg.

Sincerely,

Kenneth R. Brown, M.D.
Executive Director
Worldwide Regulatory Affairs
Biologics/Vaccines

[redacted]

TOTAL P.02

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WORLD HEALTH ORGANIZATION
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TDR Product Development

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TDR DIRECT FAX: (22) 791 48 54

4313

Message No ..4228. Page ..1... of ..1... Date: 13 August 1997

From : Dr W.E. Gutteridge,
Coordinator, TDR/TDP

To: Dr Bruce Benton
Manager, Onchocerciasis Coordination Unit
Onchocerciasis Control Programme (OCP) and
African Programme for Onchocerciasis Control (APOC)
The World Bank
1818 H Street N.W., Washington, D.C. 20433
USA

Fax No: 00 1 202 522 3587 or 202 473 8216

Our ref: **Subject:** ONCHOCERCIASIS CONTROL PROGRAMME (OCP) AND AFRICAN PROGRAMME FOR ONCHOCERCIASIS CONTROL (APOC) DONORS CONFERENCES, PARIS, OCTOBER 20-22 1997 AND DECLARATION OF INTENT, DATED JUNE 27 1997

Dear Bruce,

Thank you for your invitation to the above meetings. Unfortunately my schedule will allow me to be present in Paris only on Monday, 20 October 1997. Could the item on the external review of MACROFIL and any other MACROFIL matters be handled then? I would appreciate your understanding on this matter.

Is anyone from the Review Committee being invited. This seems a good idea to me.

Kindest regards.

Yours sincerely,

Dr W.E. Gutteridge
Coordinator
Product Research and Development
Special Programme for Research and
Training in Tropical Diseases

WORLD HEALTH ORGANIZATION
AFRICAN REGION

ORGANISATION MONDIALE DE LA SANTE
REGION DE L'AFRIQUE

ONCHOCERCIASIS CONTROL PROGRAMME IN WEST AFRICA
PROGRAMME DE LUTTE CONTRE L'ONCHOCERCOSE EN AFRIQUE DE L'OUEST
Tél.: (226) 30 23 01 - 30 23 12 - 30 23 13

Misc 833

1 IBB
2 MERG
3 EAC 2-6 June
4 Chron

Professor Dieter Stürchler
Bundesamt für Gesundheitswesen
Sektion Meldewesen Für
Infektionskrankheiten
Hessstrasse 27 E
3079 Liebefeld
Switzerland

In reply please refer to : 023/DIR/OCP/03.97
Prière de rappeler la référence :

Ouagadougou, 26 March 1997

Dear Professor Stürchler,

First of all may I thank you for acting as chairperson of the Macrofil External Review Group (MERG) at such short notice and in unfortunate circumstances. I understand that the review meeting went well, and that the draft report of the group will become available in the near future.

The Committee of Sponsoring Agencies (CSA), who are coordinating the review process, had anticipated that the MERG might wish to hold a second meeting, to finalise its conclusions once the draft report was available. If you plan to hold such a second meeting, please inform Dr Girgel in Geneva, and he will make all arrangements.

After discussion with the Chairperson of the CSA, Mr Bruce Benton, it has been decided that the report of your group should be presented to the Expert Advisory Committee (EAC) of OCP at its next meeting in Ouagadougou, from 2-6 June 1997.

I would therefore like to invite you or, if that is not possible, another member of the group to present the report to the EAC in Ouagadougou. This item will appear on the Agenda for Tuesday afternoon, 3 June, and if you are unable to attend the whole meeting it would be possible to fly to Ouagadougou during the weekend prior to the meeting, and to leave on a late flight Tuesday evening.

The costs of your travel to Ouagadougou, and per diem payments, would of course be paid by OCP according to current WHO standards.

Could you please therefore inform me, at your earliest convenience, if you can accept this invitation, and if you are unable to do so, please tell me know which member of the group will be able to present the report to the EAC.

I look forward to your reply on this matter, and thank you again for the work which you carried out on the Macrofil External Review.

Yours sincerely,

K. Yankum Dadzie

Dr K. Yankum Dadzie
Director, OCP

cc: Mr Bruce Benton, Chairperson, CSA ✔

① brief – CSA Ask Bruce Benten Edit
② CSA 74 ③ Macdfil
④ chron

REVIEW OF MACROFIL

Executive summary

❶ A macrofilaricide has not been developed. But OCT/MACROFIL has made important contributions to drug discovery and development for filarial infections.

❷ MACROFIL has greatly improved drug storage and delivery, drug testing and evaluation and brought these to international GCP/GLP (Good Clinical Practice/Good Laboratory Practice) standards.

❸ There is a continued need for a macrofilaricide for *Onchocerca volvulus* and lymphatic filariasis. There is also a need for a back up or replacement microfilaricide to sustain the OCP achievements.

❹ Development of ivermectin resistance by *Onchocerca volvulus* is a distinct possibility. Therefore resurgences of onchocerciasis in OCP control areas should be monitored and active research into the molecular basis of ivermectin resistance should be continued.
Any use of anthelmintics for filariasis must take into account possible selection for resistance in human gastrointestinal nematodes.

❺ A much greater number of compounds should be screened. In the short term a new microscreen with parasitic nematodes might enable this target to be met. Later this will be met with molecular targets.

❻ Where claims of anthelmintic activity have been made into the scientific literature, every effort should be made to obtain the compounds from the author or other sources.

❼ A full time manager based in Geneva is still required.

❽ Partnership with industry should be encouraged.

❾ The proposal for a drug development unit of the TDR to include MACROFIL is endorsed: research and development plans for a new macrofilaricidal or microfilaricidal compounds should clearly delineate the anticipated profile of the product, including its spectrum of activity, its indications, its level of efficacy and safety, its formulation and dosing, and the costs of application.

1. Review group

Professor D.W.Büttner, Hamburg, Germany.
Dr.G.C.Coles, Bristol, UK (Rapporteur)
Professor D.Stürchler, Liebefeld, Switzerland (Chairperson),
Dr .A.Venkateswarlu, Hyderabad, India.

Ivermectin is also important in *Wuchereria* where it reduces transmission. Thus the work of MACROFIL paved the way for WHO studies on the field delivery of drugs and applied field research.

MACROFIL has also sponsored valuable research on the role of albendazole in reducing microfilariae (it is superior to DEC (diethyl carbamazine)/metrifonate as it is embryocidal) and supported the development of the depot benzimidazole UMF 078. This compound is the current lead. About 1 in 100 active compounds with macro- or microfilaricidal activity can be expected to successfully complete the full research (including galenic, pharmacological and toxicological studies) and development (phases 1 to 3) process up to registration and introduction. Failures with research on leads from Ciba, Upjohn and Wellcome are not therefore surprising and MACROFIL is commended for accepting failures and stopping research on these areas. For example the Ciba-Geigy compound amocarzine (CG 6140) has been dropped for onchocerciasis but is being continued for lymphatic filariasis.

Other major contributions of MACROFIL include:
i] Arranging a data base of chemicals,
ii] Arranging reliable storage and shipping of samples and supply of information on drugs,
iii] Introducing legal contracts between WHO and industry,
iv] Ensuring TDR is becoming more professional in drug development,
v] Setting up clinical centers in Africa and Asia. Especially commended is Dr.Awadzi in Ghana who has produced more than 20 research papers since the last external review in 1987,
vi] Arranging monitoring of clinical centers and drug analytical centers to ensure that the work meets GCP/GLP standards,
vii] Developed standards for assessing damage to adult *O.volvulus* worms by drugs,
viii] Installed a macrodiagnostics laboratory which has proved successful in lymphatic filariasis.
About 200 original research papers produced through MACROFIL sponsorship have had a catalytic effect on research in this area.

The committee was very impressed by all the work that Dr.Ginger has personally undertaken to achieve these targets and results and commend him for his success in the program.

It is clear from the achievements that MACROFIL has been very effective in promoting the development of treatments, and in encouraging research on filarial nematodes. But the committee considers that a change in management structure (2.6) as proposed in the internal review would be beneficial to the program. In addition there must be a much greater testing of novel compounds.

2.2 Future Research Strategy

The committee considered that there is a continued strong need for macrofilaricidal drugs for both onchocerciasis and filariasis.

2.2.1 Risk assessment

Only three broad spectrum groups of anthelmintics (anti-nematodal drugs) have been produced by industry in the last forty years, the benzimidazoles, levamisole/morantel and the

Two approaches to monitor for resistance could be adopted.
A. Wherever resurgences of onchocerciasis occur within the OCP control area the effectiveness of ivermectin in reducing the filarial burden and in keeping the burden low for as long would be expected should be established. The latter statement is based on the finding that the first sign of resistance in veterinary nematodes can be a reduced egg reappearance period. Any validation of PCR probes for the detection of resistance will require the identification of a population of filariae showing reduced response to ivermectin.
B. The molecular basis of ivermectin resistance in populations of different species of veterinary nematodes should be established. There is an active program to produce PCR probes to detect ivermectin resistance supported by MACROFIL These will be of considerable value for use in the field and the committee therefore fully endorses this work. Obviously as soon as a molecular basis of resistance has been established research must be undertaken to see if the same mechanism could occur in *Onchocerca.*

If albendazole is to be used regularly in the control of filariae, use should be made of existing knowledge of the molecular basis of low level benzimidazole resistance in veterinary nematodes to establish whether this change could occur in filarial nematodes. It should be determined whether a small percentage of worms already have the mutation at amino acid position 200.

The chances that filarial nematodes will develop resistance to ivermectin cannot be predicted. But there have been so many examples of resistance developing to excellent drugs in other parasites that it must be assumed that ivermectin resistance will develop. The committee therefore concluded that a back up or replacement microfilaricide should be sought.

2.3 Current methodology.

Screening has been improved, for example with the inclusion of *in vitro* tests with the target organism where relevant and a switch from *O.gibsoni* to *O.ochengi* for tertiary screening. These techniques using filariae have to be continued for compounds that have shown any nematocidal efficacy. However they are not suitable for primary screening of large numbers of compounds, of unknown potential activity against nematodes. Therefore further attempts should be made to develop an assay using filarial nematodes for testing of large numbers of compounds.

As long as such a test is not available consideration should be given to the introduction of a high throughput assay using other nematodes such as the adult stage of the free living nematode *Caenorhabditis elegans* or larvae of parasitic nematodes such as *Haemonchus contortus* from sheep using a micro developmental assay as used for detecting anthelmintic resistance.

With the chances of a new drug being found estimated at around one per 10,000 compounds tested it is clear that **a much higher rate of screening of compounds must be achieved** if a novel macrofilaricide is to be discovered. Current testing is only running at about 1,000 compounds per year although it is recognized that these are usually molecules that have been preselected for potential activity rather than strictly random. Since it is accepted that there is no satisfactory high throughput screen that is likely to be developed using filarial nematodes in the near future, two alternatives are proposed:

2.4 Financial and human resources

The overall total budget since 1982 of US$29 million available to MACROFIL should be viewed against pharmaceutical industry standards which quote costs for the development of a novel drug in the order of $300 million. Given the financial limits, the committee agrees with a broad proportion of 1/3 of the budget being spent on the identification of new targets and drug screening and of 2/3 spent on preclinical development of an active compound, clinical trials and on research on ivermectin resistance. However, this broad pattern may change rapidly as specific interests or developments occur during the year.

As for manpower the committee is of the strong opinion that a full time manager should continue to be available to MACROFIL. This manager should be based in Geneva because of his or her close cooperation with academia, industry and as a member of product development at WHO. A pre-requisite for clinical trial monitor provided by the product development unit of TDR should be the knowledge and interest in filariasis. The committee recognized the use of recently retired people from industry and endorses this action.

2.5 Partnerships with industry and academia

Over the years MACROFIL has significantly contributed to improved relationships with industry. Model contracts are now available to contract out specific portions of the research or development process. It was felt that well defined tasks, such as, for example, production or toxicity testing, would have a greater chance to attract the interests of industry than large and complete programs with a relatively high risk of failure.

There was a strong case for sharing certain projects with others *e.g.* the European Union and NGOs. The successful joint funding of the *O.ochengi* project should stimulate the search for other partners.

2.6 MACROFIL reporting and line management

The committee welcomes the organizational changes within TDR and the incorporation of MACROFIL into the line management of the planned drug development unit of TDR. However care should be taken that the project manager of MACROFIL does not report to two or more different scientific and technical review committees. To simplify procedures the committee proposes that a common and standardized reporting format be agreed by all responsible committees, and that apart from technical review within TDR, overseeing committees would not review the status more than once per year.

20. Mai 1997

Signed:

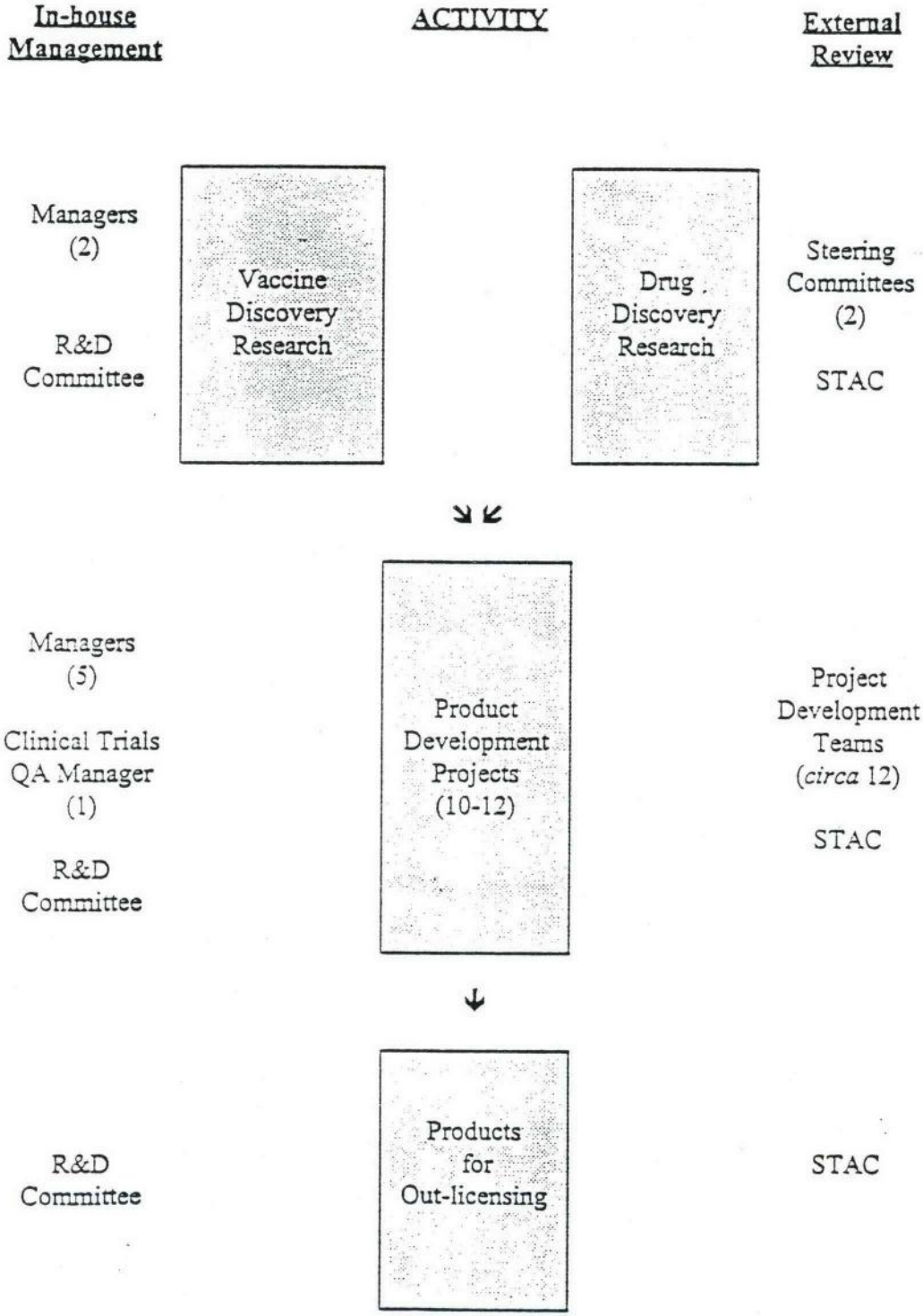
Professor D.Stürchler, Chairperson

Dr.G.C.Coles, Rapporteur

Professor D.W.Büttner

Dr.A.Venkateswarlu

STRUCTURE OF A NEW LOOK TDR/TDP



MACROFIL - Drug Screening