# ORPHAN DRUGS IN ASIA
# 2014

## Guidelines and Regulatory Requirements To Help Orphan Drug Products Enter the Asian Market

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# 1. INTRODUCTION

Thirty years ago, most pharmaceutical companies passed up the opportunity to develop drugs for rare diseases, as the low patient numbers often led to an unprofitable product. As a result, drugs for rare diseases became known as "orphan drugs," since patients were "orphaned" from the development of medications to treat their conditions. But, when one considers that approximately 7,000 rare diseases have been identified, the opportunity for orphan drug development and financial gain may be significant in some cases. However, it was not until 1983 that orphan drug development finally took off, following the implementation of the *Orphan Drug Act* by the US Food and Drug Administration (FDA), which offered financial benefits to orphan drug developers.

## 1.1 GLOBAL OUTLOOK ON RARE DISEASES

A rare disease affects a small number of people in comparison to the general population and the classification of a rare disease varies across continents, regions and countries. For instance, the FDA classifies a disease as rare if it affects less than 200,000 out of about 315 million Americans. In Japan, the Ministry of Health, Labor and Welfare states that a disease must affect less than 50,000 of the country's 127 million citizens in order to be considered rare. And, while a disease may be classified as rare in one country, the disease may be more prevalent in another country. Furthermore, the status of a disease may change over time, becoming more prevalent as doctor awareness and diagnosis abilities improve.

There are thousands of documented rare diseases and new ones are discovered on a regular basis. They are generally very serious, chronic diseases and often life-threatening. Because these diseases are unusual and affect only a limited number of people, patients generally have trouble obtaining a diagnosis, locating disease information and support, and treatment options can be limited, unavailable, or even non-existent. At times, some patients with rare diseases are never diagnosed properly and their condition remains unidentified throughout their life.

Many groups, committees and associations have been established throughout the world to provide support to rare disease patients, families and doctors. This includes emotional support, education and awareness, and sometimes, financial support. However, it is often difficult for these groups to obtain the necessary funding to improve the overall accessibility, affordability and efficacy of the treatment for a rare disease. Ultimately, sufferers of rare diseases rely on pharmaceutical companies to create new and/or improved drugs.

Pharmaceutical companies spend an estimated $35 billion annually on research and development (R&D) of new drugs. Today, the R&D of a single drug can cost up to $100 million, an increase of over 400% since 1980. However, the success rate of getting a new drug on the market is extremely small (See Table 1) and the process can often take 10-15 years. Since the potential sales of an orphan drug are limited, many pharmaceutical companies have been reluctant to develop and market them due to the possibility of

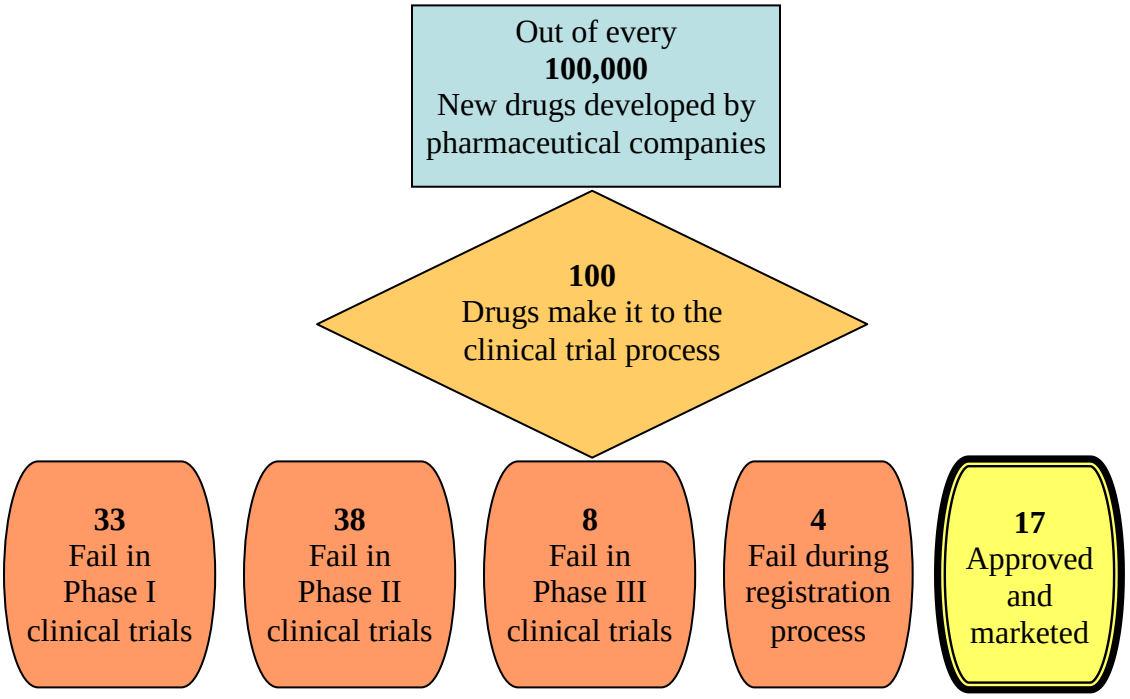
significant financial loss. Therefore, in the past, many drugs for rare diseases were developed as a response to a public health need rather than for economic purposes or financial gain by drug companies.

Nevertheless, a growing market exists for orphan drugs. Market researchers estimate that the global market for orphan drugs grew to almost $92 billion in 2013, from $50 billion in 2005. This was aided by the increasing number of approved orphan drugs by health ministries in developed countries and in more advanced Asian countries. The orphan drug market was also aided by improved medical insurance coverage and reimbursements for rare disease treatments.

With more drug discoveries to treat rare diseases, the orphan drug market is projected to grow to $120 billion by 2017. Nevertheless, the market will be skewed towards the developed western countries. For example, more than 50% of 2009's orphan drug market was accounted for by the US.

**Table 1**

## Drug Approval Statistics in the United States




*Note: These figures are estimates by Pacific Bridge Medical.*

## 1.2 DEVELOPMENT OF ORPHAN DRUG LEGISLATION

### 1.2.1 Introduction

Over the past 20 years, there has been a considerable increase in the number of orphan drugs developed for rare diseases – a result of new legislation implemented to support and encourage the development of orphan drugs. The first orphan drug legislation was passed by the FDA in 1983, called the *Orphan Drug Act* (ODA). This law classifies and regulates orphan drugs separately from other drugs, and provides numerous benefits for companies that develop and register orphan drugs with the FDA.

### 1.2.2 Definition of an Orphan Drug, According to the US FDA

According to the ODA, the FDA classifies a pharmaceutical as an orphan drug if it treats a disease which, (a) affects less than 200,000 people in the US, or (b) affects more than 200,000 people in the US, but the cost of developing and producing the drug is not expected to be recovered from the drug sales. (Note: the ODA also applies to biologicals and medical devices.) The Office of Orphan Products Development (OOPD) is responsible for overseeing the regulations of the ODA and promoting the safety and efficacy of products for treating rare diseases.

Since the ODA was passed in 1983, there were more than 2,000 applications to the FDA for orphan drugs, but only about 350 orphan drugs have been approved (for more than 420 indications). Between 1973 and 1983, less than 10 orphan drugs were approved in the US.

### 1.2.3 International Legislation

Since the ODA was passed in 1983, orphan drug legislation has been passed in several other countries and regions, including the following:

- Singapore, *Orphan Drug Exemption to the Medicines Act*, 1991
- Japan, *Orphan Drug Amendment to the Pharmaceutical Affairs Law*, 1993
- Australia, *Australian Orphan Drugs Program*, 1997
- South Korea, *Orphan Drug Act*, 1998
- European Union, *Regulation 141/2000 in the Official Journal of the European Communities*, 2000
- Taiwan, *Rare Disease and Orphan Drug Act*, 2000

The Philippines, Thailand, and India are also considering orphan drug legislation.

While sections of orphan drug legislation outside the US may be based on the US FDA's ODA, each country defines and regulates orphan drugs independently.

## 1.3 WELL-KNOWN RARE DISEASES

### 1.3.1 Duchenne Muscular Dystrophy

Duchenne Muscular Dystrophy, along with a number of other types of Muscular Dystrophy (MD), such as Becker MD, Emery Dreifuss MD and Limb Girdle MD, are currently classified as rare diseases. Duchenne MD is the most common form of MD in children and is characterized as a hereditary, degenerative disease of the skeletal muscles. A person generally starts showing signs of the disease between the ages of three and six, displaying symptoms of muscle weakness and atrophy in the pelvic and shoulder muscles. The disease then affects muscles in the trunk and forearms and by age 10 or 12, patients usually require the use of a wheelchair for mobility. In January 2005, PTC Therapeutics received orphan drug designation for PTC124, indicated to treat Duchenne MD.

### 1.3.2 Gaucher Disease

Gaucher disease is an inherited metabolic disorder with symptoms that vary greatly from case to case. In the body, certain types of fat, known as glycolipids, abnormally accumulate due to the lack of the enzyme glucocerebrosidase. This abnormal storage of lipids leads to symptoms such as an enlarged spleen or liver, anemia, or skeletal abnormalities. While Gaucher disease may cause some patients to have severe complications, other patients will be asymptomatic. Orphan drugs used to treat Gaucher disease include Ceredase (Alglucerase) and Cerezyme (Imiglucerase).

### 1.3.3 Multiple Sclerosis

Multiple Sclerosis (MS) is a disease of the central nervous system generally characterized by episodes of neurological impairment. MS is not an inherited disease, though both environmental and genetic conditions can affect one's susceptibility to the disease. Physical therapy plays a key role in the treatment of MS and depending on a patient's symptoms, they may be given medication for treatment, as well as the orphan drug Avonex (Interferon Beta 1A), Betaseron (Interferon Beta 1B) or Lioresal (Baclofen).

### 1.3.4 Narcolepsy

Narcolepsy is a disorder of the regulation of consciousness and sleep and occurs in approximately 0.05% of the population. The onset of narcolepsy can occur in childhood or as late as age 50, with characteristics ranging from sleep paralysis to hallucinations. While the disease is incurable, the orphan drug Modafinil is often prescribed to help control the disease.

## 1.4 US FDA CONTACT INFORMATION

Food and Drug Administration

Address: 10903 New Hampshire Avenue, Silver Spring, MD 20993
Phone: 1-888-463-6332
Website: http://www.fda.gov

Office of Orphan Products Development, Food and Drug Administration

Address: 10903 New Hampshire Avenue, Silver Spring, MD 20993
Phone: 301-796-8660 / 1-800-300-7469
Fax: 301-847-8621
Email: orphan@fda.hhs.gov; Jeff Fritsch, jeff.fritsch@fda.hhs.gov (orphan drug designations)
Phone (Jeff Fritsch): 301-827-0989
Website: http://www.fda.gov/orphan/index.htm

## 1.5 US ORPHAN DRUG ASSOCIATIONS

Genetic and Rare Conditions Site, University of Kansas Medical Center

Address: 3901 Rainbow Blvd., Kansas City, KN, 66160
Email: dcollins@kumc.edu (Debra Collins, M.S. CGC**)**
Website: http://www.kumc.edu/gec/support

*The Genetic and Rare Conditions Site provides information on genetic conditions, including a list of conditions and support groups/organizations.*

Genetic Alliance, Inc.

Address: 4301 Connecticut Ave., N.W., Suite 404, Washington, D.C. 20008
Phone: 202-966-5557
Fax: 202-966-8553
Email: info@geneticalliance.org
Website: http://www.geneticalliance.org

*An international coalition founded in 1986, it is comprised of more than 600 advocacy and healthcare organizations supporting individuals with genetic conditions.*

National Organization for Rare Disorders

Address: 55 Kenosia Avenue, Danbury, CT 06810
Phone: 1-800-999-6673 or 203-744-0100 (international)
Fax: 203-798-2291

Email: orphan@rarediseases.org
Website: http://www.rarediseases.org

*The National Organization for Rare Disorders (NORD) was founded in 1983 as a non-profit health agency to support rare disease patients and their families. NORD provides information and education about rare diseases, referrals to organizations and research grants.*

Madisons Foundation

Address: P.O. Box 241956, Los Angeles, CA 90024
Phone: 310-264-0826
Fax: 310-264-4766
E-mail: getinfo@madisonsfoundation.org
Website: http://www.madisonsfoundation.org

*Madisons Foundation was established to improve the lives of children with rare diseases and their families through increased rare disease research and education.*

Office of Rare Diseases Research, National Institutes of Health

Address: 6700 Democracy Blvd, Suite 1001, Bethesda, MD 20892
Phone: 301-402-4336
Fax: 301-480-9655
Email: ordr@od.nih.gov
Website: http://rarediseases.info.nih.gov

*The Office of Rare Diseases (ORDR) was established in 1993 within the Office of the Director of the National Institutes of Health (NIH). ORDR works with the NIH to encourage and coordinate the research of rare diseases through support activities such as grant programs, scientific conferences and regional workshops.*

Genetic and Rare Diseases Information Center

Address: P.O. Box 8126, Gaithersburg, MD 20898-8126
Phone: 1-888-205-2311 or 301-251-4925 (international calls)
Fax: 301-251-4911
Website: http://rarediseases.info.nih.gov/GARD
Email: (email form on above website)

*The Genetic and Rare Diseases Information Center provides information on genetic and rare diseases for patients, health professionals and healthcare researchers. The organization was established by two National Institutes of Health agencies: The National Human Genome Research Institute and the Office of Rare Diseases Research.*

## 1.6 US FDA ORPHAN DRUG APPROVALS (JANUARY 2002 TO MARCH 2014)

| Marketing Approval | Generic Name | Trade Name | Designation (may be abbreviated) | Orphan Designation | Company |
|---|---|---|---|---|---|
| 1/18/2002 | Nitisinone | Orfadin | Adjunctive therapy to dietary restriction of tyrosine and phenyllalanine in the treatment of hereditary tyrosinemia type 1 | 5/16/1995 | Swedish Orphan AB |
| 2/1/2002 | Imatinib Mesylate | Gleevec | Treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST) | 11/1/2001 | Novartis Pharmaceuticals Corp. |
| 2/19/2002 | Ibritumomab Tiuxetan | Zevalin | Treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma, including patients with Rituximab (Rituxan) refractory follicular non-Hodgkin's lymphoma | 9/6/1994 | Biogen IDEC Inc. |
| 4/4/2002 | Synthetic Porcine Secretin | Synthetic Porcine Secretin | Use in secretin stimulation for stimulation of pancreatic secretions, including bicarbonate, to aid in the diagnosis of pancreatic exocrine dysfunction | 3/7/2000 | ChiRhoClin, Inc. |
| 4/4/2002 | Synthetic Porcine Secretin | Synthetic Porcine Secretin | Use in secretin stimulation testing for stimulation of gastrin secretion to aid in the diagnosis of gastrinoma | 6/19/1999 | ChiRhoClin, Inc. |
| 5/21/2002 | Treprostinil | Remodulin | Treatment of pulmonary arterial hypertension | 6/4/1997 | United Therapeutics Corp. |
| 7/12/2002 | Rasburicase | Elitek | Initial management of plasma uric acid levels in pediatric patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anti-cancer therapy expected to result in tumor lysis and subsequent elevation of plasma uric acid | 10/11/2000 | Sanofi-Synthelabo Research |
| 7/17/2002 | Oxybate | Xyrem | Treatment of cataplexy associated with narcolepsy | 11/7/1994 | Orphan Medical, Inc. |
| 10/8/2002 | Buprenorphine Hydrochloride | Subutex | Treatment of opioid dependence in patients 16 years of age or older | 6/15/1994 | Reckitt Benckiser Pharmaceuticals, Inc. |
| 10/8/2002 | Buprenorphine in combination with Naloxone | Suboxone | Treatment of opioid dependence in patients 16 years of age or older | 10/27/1994 | Reckitt Benckiser Pharmaceuticals, Inc. |

| Marketing Approval | Generic Name | Trade Name | Designation (may be abbreviated) | Orphan Designation | Company |
|---|---|---|---|---|---|
| 11/1/2002 | Synthetic Porcine Secretin | Synthetic Porcine Secretin | For use in secretin stimulation testing for: stimulation of pancreatic secretions to facilitate the identification of the ampulla of Vater and accessory papilla during endoscopic retrograde cholangio-pancreatography (ERCP) | 6/18/1999 | ChiRhoClin, Inc. |
| 11/22/2002 | Nitazoxanide | Alinia | Treatment of diarrhea caused by Cryptosporidium parvum and Giardia lamblia | 12/12/1996 | Romark Laboratories, L.C. |
| 12/20/2002 | Icodextrin 7.5% with Electrolytes Peritoneal Dialysis Solution | Extraneal (with 7.5% Icodextrin) Peritoneal Dialysis solution | For use as a single daily exchange for the long (8-16 hour) dwell during continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD) for the management of chronic renal failture | 7/18/1997 | Baxter Healthcare Corp. |
| 2/25/2003 | Polifeprosan 20 with Carmustine | Gliadel | Expanding the indication to include patients with malignant glioma undergoing primary surgical resection | 12/13/1989 | Guilford Pharmaceuticals, Inc. |
| 3/25/2003 | Pegvisomant | Somavert | Treatment of acromegaly in patients who have had an inadequate response to surgery and/or radiation therapy and/or other medical therapies, or for whom these therapies are not appropriate | 6/24/1997 | Sensus Corp. |
| 4/24/2003 | Ceramide Trihexosidase/ Alpha-galactosidase A | Fabrazyme | For use in patients with Fabry's disease to reduce globotriaosyl-ceramide (GL-3) deposition in capillary endothelium of the kidney and certain other cell types | 1/19/1988 | Genzyme Corp. |
| 4/30/2003 | Laronidase | Aldurazyme | Treatment of patients with Hurler and Hurler-Scheie forms of Mucopolysaccharidosis-I (MPS I) and for patients with the Scheie form who have moderate to severe symptoms. | 9/24/1997 | BioMarin Pharmaceutical, Inc. |
| 5/13/2003 | Bortezomib | VELCADE | Treatment of multiple myeloma patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy | 1/15/2003 | Millennium Pharmaceuticals, Inc. |

| Marketing Approval | Generic Name | Trade Name | Designation (may be abbreviated) | Orphan Designation | Company |
|---|---|---|---|---|---|
| 6/27/2003 | Tositumomab and Iodine I 131 Tositumomab | Bexxar | Treatment of patients with CD20 positive, follicular, non-Hodgkin's lymphoma, with and without transformation, whose disease is refractory to Rituximab and has relapsed following chemotherapy | 5/16/1994 | GlaxoSmithKline |
| 7/29/2003 | Ribavirin | Rebetol | Treatment of chronic hepatitis C among previously untreated pediatric patients at least three years of age or older | 4/4/2003 | Schering Corp. |
| 7/31/2003 | Miglustat | Zavesca | Treatment of mild to moderate Type I Gaucher disease in adults for whom enzyme replacement therapy is not a therapeutic option (e.g. due to constraints such as allergy, hypersensitivity, or poor venous access) | 5/29/1998 | Actelion Pharmaceuticals Ltd. |
| 8/1/2003 | Porfimer | Photofrin | For the ablation of High-Grade Dysplasia in Barrett's Esophagus in patients who not do undergo esophagectomy | 10/19/2001 | Axcan Scandipharm Inc. |
| 10/2/2003 | Iron(III)-Hexacyanoferrate(II) | Radiogardase | Treatment of patients with known or susupected internal contamination with radioactive cesium and/or radioactive or non-radioactive thallium to increase their rates of elimination | 5/1/2003 | Heyl Chemisch-Pharmzeutische Fabrik GMBH & Co. |
| 10/23/2003 | Botulism Immune Globulin | BabyBIG | Indicated for treatment of infant botulism caused by type A or type B Clostridium botulinum | 1/31/1989 | California Dept. of Health Services |
| 12/1/2003 | Somatropin [rDNA] | Zorbtive | Treatment of short bowel syndrome in patients receiving specialized nutritional support | 3/6/1995 | Serono Laboratories, Inc. |
| 1/23/2004 | Acetylcysteine | Acetadote | For the use of Acetadote™ injection, administered intravenously within 8-10 hours after ingestion of a potentially heptotoxic quantity of acetaminophen, to prevent or lesson hepatic injury | 10/19/2001 | Cumberland Pharmaceuticals, Inc. |
| 2/4/2004 | Pemetrexed Disodium | Alimta | Treatment of malignant pleural mesothelioma whose disease is either unresectable or who are otherwise not candidates for curative surgery | 8/28/2001 | Eli Lilly and Co. |
| 3/8/2004 | Cinacalcet | Sensipar | Treatment of hypercalcemia in patients with parathyroid carcinoma | 5/12/2003 | Amgen, Inc. |

| Marketing Approval | Generic Name | Trade Name | Designation (may be abbreviated) | Orphan Designation | Company |
|---|---|---|---|---|---|
| 4/20/2004 | Apomorphine HCl | Apokyn | For the acute, intermittent treatment of hypomobility, "off" episodes ("end-of-dose-wearing-off" and unpredictable "on/off" episodes) associated with advanced Parkinson's disease | 4/22/1993 | Mylan Bertek Pharmaceuticals, Inc. |
| 5/17/2004 | Tinidazole | Tindamax | Treatment of intestinal amebiasis and amebic liver abcess caused by E. histolytica in both adults and pediatric patients older than three years of age. It is not indicated for the treatment of asymptomatic cyst passage | 8/20/2003 | Presutti Laboratories, Inc. |
| 5/17/2004 | Tinidazole | Tindamax | Treatment of giardiasis caused by G. duodenalis (also termed G. lamblia) in both adults and pediatric patients older than three years of age | 4/18/2002 | Presutti Laboratories, Inc. |
| 1/15/2003 | Bortezomib | *Velcade* | Treatment of multiple myeloma patients who have received at least one prior therapy | 1/15/2003 | Millennium Pharmaceuticals, Inc. |
| 5/19/2004 | Azacitidine | Vidaza | Treatment of patients with the following myelodysplastic syndrome subtypes: refractory anemia or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia and requiring transfusions), refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic | 12/3/2001 | Pharmion Corp. |
| 6/10/2004 | Glutamine | NutreStore | Treatment of short bowel syndrome in patients receiving specialized nutritional support when used in conjunction with a recombinant human growth hormone that is approved for this indication | 3/6/1995 | Nutritional Restart Pharmaceutical, L.P. |
| 8/11/2004 | Diethylenetriamine-Pentaacetic Acid (DTPA) | Pentate Trisodium injection | Treatment of internal contamination with plutonium, americium or curium | 4/28/2004 | Hameln Pharmaceuticals GMBH |
| 9/9/2004 | Multi-vitiam Infusion without Vitamin K | M.V.I.-12 | Prevention of vitamin deficiency and thromboembolic complications in people receiving home parenteral nutrition and wafarin-type anticoagulant therapy | 3/8/2004 | Mayne Pharma (USA) Inc. |

| Marketing Approval | Generic Name | Trade Name | Designation (may be abbreviated) | Orphan Designation | Company |
|---|---|---|---|---|---|
| 10/8/2004 | Recombinant Human Luteinizing Hormone | Luveris | Luveris (lutropin alfa for injection), concomitantly administered with Gonal-f (follitrophin alfa for injection), is indicated for stimulation of follicular development in infertile hypogonadotrophic hypogonadal women with profound LH deficiency (LH less than 1.2 IU/L) | 10/7/1994 | Serono Laboratories, Inc. |
| 12/28/2004 | Clofarabine | Clolar | Treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens | 2/7/2002 | Genzyme Corp. |
| 12/29/2004 | Iloprost Inhalation Solution | Ventavis | Treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III or IV symptoms | 8/17/2004 | CoTherix, Inc. |
| 2/17/2005 | Benzoate/ Phenylacetate | Ammonul | Adjunctive therapy in the treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle | 11/22/1993 | Medicis Pharmaceutical Corp. |
| 2/18/2005 | Vaccinia Immune Globulin (Human) Intravenous | Vaccinia | Treatment and modification of aberrant infections induced by vaccinia virus that include its accidental implantation in eyes (except in cases of isolated keratitis), mouth, or other areas where vaccinia infection would constitute a special hazard; exzema vaccinia; progressive vaccinia; severe generalized vaccinina, and vaccinia infections in individuals who have skin conditions such as burns, impetigo, varicella-zoster, or poison ivy; or in individuals who have exzematous skin lesions because of either the activity or extensiveness of such lesions | 6/18/2004 | DynPort Vaccine Co. LLC |
| 2/18/2005 | Vaccinia Immune Globulin (Human) Intravenous | -- | Treatment of severe complications from the smallpox vaccine | 6/18/2004 | DynPort Vaccine Company LLC |
| 3/15/2005 | Temozolomide | Temodar | Treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherpay and then as maintenance treatment | 10/5/1998 | Schering-Plough Research Institute |

| Marketing Approval | Generic Name | Trade Name | Designation (may be abbreviated) | Orphan Designation | Company |
|---|---|---|---|---|---|
| 4/8/2005 | Fluocinolone | Retisert | Treatment of chronic non-infectious uveitis affecting the posterior segment of the eye | 7/31/2000 | Bausch & Lomb Pharmaceuticals, Inc. |
| 5/31/2005 | N-acetylgalactosamine-4-sulfatase, recombinant human | Naglazyme | Treatment of mucopolysaccharidosis Type VI (Maroteaux-Lamy syndrome) | 2/17/1999 | BioMarin Pharmaceutical, Inc. |
| 7/11/2005 | Coagulation factor VIIa (recombinant) | NovoSeven | Prevention of bleeding in surgical interventions or invasive procedures in patients with congenital F VII deficiency | 9/10/2004 | Novo Nordisk, Inc. |
| 7/11/2005 | Coagulation factor VIIa (recombinant) | NovoSeven | Treatment of bleeding episodes in patients with Factor VII Deficiency | 9/10/2004 | Novo Nordisk, Inc. |
| 8/11/2005 | Meloxicam | Mobic | Treatment of juvenile rheumatoid arthritis | 11/22/2002 | Boehringer Ingelheim Pharmaceuticals, Inc. |
| 8/12/2005 | Coagulation factor VIIa (recombinant) | NovoSeven | Prevention of bleeding in surgical interventions or invasive procedures in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX | 6/18/2004 | Novo Nordisk, Inc. |
| 8/12/2005 | Quinine Sulfate | -- | Treatment of malaria | 6/3/2004 | AR Holding Company, Inc. |
| 8/30/2005 | Mecasermin | Increlex | Treatment of growth hormone insensitivity syndrome | 12/12/1995 | Tercica, Inc. |
| 10/28/2005 | Nelarabine | Arranon | Treatment of acute lymphoblastic leukemia and lymphoblastic lymphoma | 8/10/2004 | GlaxoSmithKline |
| 11/2/2005 | Deferasirox | Exjade | Treatment of chronic iron overload in patients with transfusion-dependent anemias | 11/21/2002 | Novartis |
| 11/18/2005 | Oxybate | Xyrem | Treatment of narcolepsy | 11/7/1994 | Jazz Pharmaceuticals |
| 12/12/2005 | mecasermin rinfabate | iPLEX | Treatment of growth hormone insensitivity syndrome (GHIS) | 5/17/2002 | Insmed, Inc. |
| 12/20/2005 | Sorafenib | Nexavar | Treatment of renal cell carcinoma | 10/8/2004 | Bayer Pharmaceutical Corporation |
| 12/27/2005 | Lenalidomide | Revlimid | Treatment of myelodysplastic syndromes | 12/27/2005 | Celgene Corporation |
| 3/1/2006 | Cetuximab | Erbitux | Treatment of squamous cell cancer of the head and neck in patients who express epidermal growth factor receptor | 7/3/2000 | ImClone Systems Incorporated |
| 3/29/2006 | Tacrolimus | Prograf | Prophylaxis of organ rejection in patients receiving heart transplants. | 6/6/2005 | Astellas Pharma US, Inc. |

| Marketing Approval | Generic Name | Trade Name | Designation (may be abbreviated) | Orphan Designation | Company |
|---|---|---|---|---|---|
| 4/13/2006 | Ibuprofen lysine | NeoProfen | Treatment of patent ductus arteriosus | 10/29/1996 | Farmacon-IL, LLC |
| 4/28/2006 | Recombinant human acid alpha-glucosidase | Myozyme | Treatment of glycogen storage disease type II | 8/19/1997 | Genzyme Corporation |
| 5/2/2006 | Decitabine | Dacogen | Treatment of myelodysplastic syndromes | 3/8/1999 | MGI CP, Inc. |
| 5/19/2006 | Infliximab | REMICADE | Treatment of pediatric (0 to 16 years of age) Crohn's Disease | 11/12/2003 | Centocor, Inc. |
| 5/25/2006 | Thalidomide | Thalomid | Treatment of multiple myeloma | 10/14/1998 | Celgene Corporation |
| 6/28/2006 | Dasatinib | Sprycel | Treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia with resistance or intolerance to prior therapy | 11/18/2005 | Bristol-Myers Squibb |
| 6/28/2006 | Dasatinib | Sprycel | Treatment of chronic myelogenous leukemia | 11/28/2005 | Bristol-Myers Squibb |
| 6/29/2006 | Lenalidomide | Revlimid | Treatment for multiple myeloma | 9/20/2001 | Celgene Corporation |
| 7/24/2006 | Idursulfase | Elaprase | Long term enzyme replacement therapy for patients with MPS II (Hunter Syndrome) | 11/28/2001 | Shire Human Genetic Therapies, Inc. |
| 7/26/2006 | Biocarbonate infusate | Normocarb HF | Use as a replacement solution in Continuous Renal Replacement Therapy (CRRT) to replace water and to correct electrolytes and acid-base imbalances in adults and children | 8/9/2005 | Dialysis Solutions, Inc. |
| 10/6/2006 | Vorinostat | Zolinza | Treatment of T-cell non-Hodgkin's lymphoma | 3/16/2004 | Merck & Co., Inc. |
| 10/19/2006 | Imatinib mesylate | Gleevec | Treatment of systemic mastocytosis without the D816V c-kit mutation | 9/9/2005 | Novartis |
| 10/19/2006 | Imatinib mesylate | Gleevec | Treatment of myeloproliferative disorders/myelodysplastic syndromes associated with platelet-derived growth factor gene re-arrangements | 10/5/2005 | Novartis |
| 10/19/2006 | Imatinib mesylate | Gleevec | Treatment of idiopathic hypereosinophilic syndrome including acute and chronic eosinophilic leukemia | 8/25/2005 | Novartis |
| 10/19/2006 | Imatinib mesylate | Gleevec | Treatment of Philadelphia-positive acute lymphoblastic leukemia | 10/11/2005 | Novartis |
| 10/19/2006 | Imatinib mesylate | Gleevec | Treatment of dermatofibrosarcoma protuberans | 12/19/2005 | Novartis |
| 12/15/2006 | Hydroxocobalamin | Cyanokit | Treatment of acute cyanide poisoning | 11/25/2003 | EMD Pharmaceuticals, Inc. |

| Marketing Approval | Generic Name | Trade Name | Designation (may be abbreviated) | Orphan Designation | Company |
|---|---|---|---|---|---|
| 12/20/2006 | Balsalazide disodium | Colazal | Treatment of pediatric patients with ulcerative colitis | 8/12/2005 | Salix Pharmaceuticals, Inc. |
| 1/31/2007 | Antihemophilic factor (Human) | Alphanate | Treatment of von Willebrand's disease | 1/5/1996 | Grifols Biologicals Inc. |
| 3/16/2007 | Eculizumab | Soliris | Treatment of paroxysmal nocturnal hemoglobinuria | 8/20/2003 | Alexion Pharmaceuticals, Inc. |
| 3/30/2007 | Protein C concentrate | Ceprotin | For replacement therapy in congenital protein C deficiency for the prevention and treatment of thrombosis, pulmonary emboli, and purpura fulminans | 6/23/1992 | Baxter Healthcare Corporation |
| 4/6/2007 | Hepatitis B immune globulin (human) | HepaGam | Prevention of hepatitis B recurrence following orthotopic liver transplant | 3/24/2008 | Cangene Corporation |
| 5/3/2007 | Histrelin | Supprelin LA | Treatment of central precocious puberty | 11/18/2005 | Indevus Pharmaceuticals |
| 5/17/2007 | Doxorubicin HCL liposome injection | Doxil | Treatment of multiple myeloma | 12/29/2004 | Johnson & Johnson Pharmaceutical Research & Dev. |
| 5/30/2007 | Temsirolimus | Torisel | Treatment of renal cell carcinoma | 12/16/2004 | Wyeth Pharmaceuticals |
| 5/31/2007 | Somatropin | Norditropin | Treatment of short stature in patients with Noonan syndrome | 8/9/2006 | Novo Nordisk Inc. |
| 6/15/2007 | Ambrisentan | Letairis | Treatment of pulmonary arterial hypertension | 7/16/2004 | Gilead Colorado |
| 8/30/2007 | Lanreotide | Somatuline Depot | Treatment for acromegly | 9/11/2000 | IPSEN, Inc. |
| 9/6/2007 | Dexrazoxane | Totect | Treatment of anthracycline extravasation during chemotherapy | 3/25/2004 | Topo Target A/S |
| 9/13/2007 | Raloxifene | Evista | Reduction of the risk of breast cancer in postmenopausal women | 7/14/2005 | Eli Lilly and Company |
| 10/29/2007 | Nilotinib | Tasigna | Treatment of chronic myelogenous leukemia | 4/27/2006 | Novartis |
| 12/13/2007 | Sapropterin | Kuvan | Treatment of hyperphenylalaninemia | 1/29/2004 | Biomarin Pharmaceutical Inc. |
| 12/14/2007 | Thyrotropin alfa | Thyrogen | Treatment of well-differentiated papillary, follicular or combined papillary/follicular carcinomas of the thyroid | 8/3/2001 | Genzyme Corporation |
| 2/21/2008 | Adalimumab | Humira | Treatment of juvenile rheumatoid arthritis | 3/21/2005 | Abbott Laboratories |

| Marketing Approval | Generic Name | Trade Name | Designation (may be abbreviated) | Orphan Designation | Company |
|---|---|---|---|---|---|
| 2/27/2008 | Rilonacept | Arcalyst | Treatment of CIAS1-Associated Periodic Syndromes | 12/20/2004 | Regeneron Pharmaceuticals, |
| 3/7/2008 | Levoleucovorin | Fusilev | For use in conjunction with high-dose methotrexate in the treatment of osteosarcoma. | 8/1/1991 | Spectrum Pharmaceuticals |
| 3/20/2008 | Bendamustine hydrochloride | Treanda | Treatment of chronic lymphocytic leukemia | 8/17/2007 | Cephalon, Inc. |
| 8/15/2008 | Tetrabenazine | Xenazine | Treatment of Huntington's disease | 12/11/1997 | Prestwick Pharmaceuticals, Inc |
| 8/22/2008 | Romiplstim | Nplate | Treatment of immune thrombocytopenic purpura | 3/27/2003 | Amgen, Inc. |
| 9/12/2008 | Immune Globulin (Human) | Gamunex | Treatment of chronic inflammatory demyelinating polyneuropathy | 7/27/2004 | Talecris |
| 9/19/2008 | Iobenguane I 123 | Adreview | For the diagnosis of pheochromocytomas | 12/1/2006 | GE Healthcare, Inc. |
| 9/19/2008 | Iobenguane I 123 | Adreview | For the diagnosis of neuroblastomas | 12/1/2006 | GE Healthcare, Inc. |
| 10/10/2008 | C1 Esterase Inhibitor (Human) | Cinryze | Treatment of angioedema | 7/16/2004 | ViroPharma Biologics Incorporated |
| 11/14/2008 | Rufinamide | Banzel | Treatment of Lennox-Gastaut Syndrome | 10/08/2004 | Eisai, Inc. |
| 11/20/2008 | Eltrombopag | Promacta | Treatment of idiopathic thrombocytopenia purpura | 5/5/2008 | GlaxoSmithKline |
| 12/15/2008 | Plerixafor | Mozobil | To improve the yield of progentor cells in the apheresis product for subsequest stem cell transplantation following certain chemotherapies | 7/10/2003 | Genzyme Corporation |
| 12/18/2008 | Fludarabine Phosphate Oral Tablets | -- | Treatment of B-cell chronic lymphocytic leukemia | 12/18/2007 | sanofi-aventis U.S. |
| 1/16/2009 | Human Fibrinogen Concentrate, Pasteurized | Riastap | Treatment of fibrinogen deficient patients | 3/13/2008 | CSL Behring, LLC |
| 2/6/2009 | Recombinant Human Antithrombin | Atryn | Treatment of congenital antithrombin deficiency to prevent the occurrence of potentially life-threatening venous thromboembolisms | 12/7/2007 | GTC Biotherapeutics, Inc. |
| 2/20/2009 | Trypan Blue | Membraneblue | Selectively staining epiretinal membranes during ophthalmic surgical victrectomy procedures | 8/2/2006 | Dutch Ophthalmic Research Center Int'l BV |
| 4/7/2009 | Artemether/Lumefantrine | Coartem | For the treatment of infections due to Plasmodium falciparum or mixed infections | 8/31/2007 | Novartis Pharmaceuticals |
| 5/5/2009 | Bevacizamab | Avastin | Treatment of malignant glioma | 5/26/2006 | Genentech, Inc. |
| 5/22/2009 | Tadalafil | Adcirca | Treatment of pulmonary arterial hypertension | 12/18/2006 | Eli Lilly and Company |

| Marketing Approval | Generic Name | Trade Name | Designation (may be abbreviated) | Orphan Designation | Company |
|---|---|---|---|---|---|
| 6/17/2009 | Canakinumab | Ilaris | Treatment of cryopyrin-associated periodic syndromes | 12/18/2007 | Novartis Pharmaceuticals |
| 7/2/2009 | Sotalol (Iv) | So-Aqueous | For ventricular tachycardia, ventricular fibrillation, or the maintenance of sinus rhythm when oral administration is not possible | 7/25/2008 | Academic Pharmaceuticals |
| 7/29/2009 | Colchicine | Colcrys | Treatment of familial Mediterranean fever | 9/25/2007 | AR Holding Company, Inc. |
| 8/21/2009 | Vigabatrin | Sabril | Treatment of infantile spasms | 6/12/2000 | H. Lundbeck A/S |
| 9/15/2009 | Ganciclovir | Zirgan | Treatment of acute herpetic keratitis (dendritic and geographic ulcers) | 3/22/2007 | Sirion Therapeutics, Inc. |
| 9/25/2009 | Pralatrexate | Folotyn | Treatment of T-cell lymphoma | 7/20/2006 | Allos Therapeutics, Inc. |
| 10/8/2009 | C1-Esterase-Inhibitor, Human, Pasteurized | Berinert P | Prevention and/or treatment of acute attacks of hereditary angioedema | 10/16/1992 | CSL Behring L.L.C. |
| 11/5/2009 | Romidepsin | Istodax | Treatment of non-Hodgkin T-cell lymphomas | 9/30/2004 | Gloucester Pharmaceuticals, Inc. |
| 11/16/2009 | Capsaicin | Qutenza | Management of neuropathic pain in patients with postherpetic neuralgia | 5/22/2009 | NeurogesX, Inc. |
| 12/1/2009 | Ecallantide | Kalbitor | Treatment of angioedema | 2/4/2003 | Dyax Corp |
| 12/4/2009 | Human Plasma Coagulation Factor Viii And Human Plasma Von Willebrand Factor | Wilate(R) | Treatment of von Willebrand disease except for surgical/invasive procedures in patients with von Willebrand disease in whom desmopressin is either ineffective or contraindicated | 4/18/2007 | Octapharma USA, Inc. |
| 1/22/2010 | Dalfampridine | Ampyra | Treatment of walking in multiple sclerosis patients | 6/2/1987 | Acorda Therapeutics |
| 2/2/2010 | Collagenase Clostridium Histolyticum | Xiaflex | Treatment of adults with Dupuytren's contracture with a palpable cord | 5/23/1996 | Auxilium Pharmaceuticals, Inc. |
| 2/18/2010 | Rituximab | Rituxan | Treatment of patients untreated for CD20-positive chronic lymphocytic leukemia in combination wih fludarbine and cyclophosphamide | 1/29/2004 | Genentech, Inc. |
| 2/22/2010 | Aztreonam | Cayston | Inhalation therapy for control of gram-negative bacteria in cystic fibrosis patients | 3/12/2002 | Gilead Sciences (formerly Corus Pharma) |
| 2/26/2010 | Velaglucerase-Alfa | Vpriv | Treatment of Gaucher disease | 6/8/2009 | Shire Human Genetics Therapies, Inc. |

| Marketing Approval | Generic Name | Trade Name | Designation (may be abbreviated) | Orphan Designation | Company |
|---|---|---|---|---|---|
| 3/18/2010 | Carglumic Acid | Carbaglu | Adjunctive therapy for acute hyperammonemia treatment and manitenance therapy for chronic hyperammonemia | 1/20/1998 | Orphan Europe |
| 3/24/2010 | Rifaximin | Normix | Treatment to reduction risks of overt hepatic encephalopathyrecurrence in adult patients | 2/10/1998 | Salix Pharmaceuticals, Inc. |
| 3/24/2010 | Tenofovir | Viread | Treatment of HIV infection combined with other antiretroviral agents in adolescent patients | 3/17/2009 | Gilead Sciences, Inc. |
| 7/28/2010 | Glycopyrrolate | Cuvposa | Treatment of reducing chronic drooling in young patients with neurologic conditions associated with drooling problems | 6/9/2006 | Sciele Pharma, Inc |
| 9/14/2010 | Pegloticase | Krystexxa | Treatment of chronic gout in adult patients | 2/21/2001 | Savient Pharmaceuticals, Inc. |
| 9/24/2010 | Dexamethasone Intravitreal Implant | Ozurdex | Treatment of non-infectious ocular inflammation, or uveitis | 9/11/1998 | Allergan |
| 10/15/2010 | Repository Corticotropin Or Adrenocorticotropic Hormone | H.P. Acthar Gel | Treatment of infantile spasms | 5/21/2003 | Questcor Pharmaceuticals, Inc. |
| 10/20/2010 | Trastuzumab | Herceptin | Treatment of patients with HER2 | 10/13/2009 | Genentech, Inc |
| 10/29/2010 | Everolimus | Afinitor | Treatment of subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis | 6/8/2009 | Novartis Pharmaceuticals |
| 1/14/2011 | Sodium Nitrite And Sodium Thiosulfate | Nithiodote | Treatment of life-threatening cyanide poisoning | 4/9/2008 | Hope Pharmaceuticals |
| 1/28/2011 | Gabapentin | Gralise | For the management of postherpetic neuralgia. | 11/8/2010 | Depomed, Inc. |
| 2/3/2011 | Hydroxyprogesterone Caproate | Makena | Treatment to reduce risks of preterm birth in women with singleton pregnancy | 1/25/2007 | KV Pharmaceutical Company |
| 2/17/2011 | Factor XIII Concentrate | Corifact | Prophylactic treatment of congenital factor XIII deficiency | 1/16/1985 | CSL Behring LLC |
| 2/25/2011 | Cinacalcet | Sensipar | Treatment of severe hypercalcemia in patients with primary hyperparathyroidism | 4/30/2010 | Amgen, Inc |
| 3/25/2011 | Ipilimumab | Yervoy | Treatment of unresectable or metastatic melanoma | 6/3/2004 | Bristol-Myers Squibb |
| 3/29/2011 | Peginterferon alfa-2b | Sylatron | Adjuvant treatment of melanoma with microscopic or gross nodal involvement | 4/9/2008 | Schering-Plough Corporation |

| Marketing Approval | Generic Name | Trade Name | Designation (may be abbreviated) | Orphan Designation | Company |
|---|---|---|---|---|---|
| 4/6/2011 | Vandetanib | Caprelsa(R) | Treatment of asymptomatic or progressive medullary thyroid cancer | 10/21/2005 | AstraZeneca Pharmaceutical LP |
| 4/19/2011 | Rituximab | Rituxan | For treatment of patients with Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA). | 2/14/2006 | Genentech, Inc. |
| 4/29/2011 | Levoleucovorin | Fusilev | For use in combination chemotherapy with 5-fluorouracil in the palliative treatment of patients | 12/18/1990 | Spectrum Pharmaceuticals, Inc. |
| 5/5/2011 | Everolimus | Afinitor | Treatment of progressive neuroendocrine tumors of pancreatic origin (PNET) | 2/14/2008 | Novartis Pharmaceuticals Corporation |
| 6/15/2011 | Belatacept | Nulojix | Prophylaxis of organ rejection in adult patients receiving kidney transplants | 2/20/2008 | Bristol-Myers Squibb Company |
| 7/29/2011 | Coccidioidin SD Skin Test Antigen | -- | For the detection of delayed type hypersensitivity to C. immitis | 12/19/2007 | Allermed Labortories, Inc. |
| 8/4/2011 | Centruroides immune F(ab)2 | Anascorp | Treatment of clinical signs of scorpion envenomation | 6/12/2000 | Rare Disease Therapeutics, Inc. |
| 8/17/2011 | Vemurafenib | Zelboraf | Treatment of unresectable or metastatic melanoma with the BRAFV600E mutation | 12/20/2010 | Hoffmann-La Roche, Inc. |
| 8/19/2011 | Brentuximab vedotin | Adcetris | The treatment of patients with systemic anaplastic large cell lymphoma (sALCL) | 10/23/2008 | Seattle Genetics, Inc. |
| 8/19/2011 | Brentuximab vedotin | Adcetris | The treatment of patients with Hodgkin lymphoma | 1/30/2007 | Seattle Genetics, Inc. |
| 8/25/2011 | Icatibant | Firazyr | Treatment of acute attacks of hereditary angioedema in adults 18 years of age and older | 11/25/2003 | Shire Orphan Therapies |
| 8/26/2011 | Crizotinib | Xalkori | Treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) | 9/13/2010 | Pfizer, Inc. |
| 9/23/2011 | Infliximab | Remicade | Treatment of pediatric patients with moderately to severely active ulcerative colitis | 11/12/2003 | Janssen Biotech Inc. |
| 9/23/2011 | Eculizumab | Soliris | For the treatment of atypical Hemolytic Uremic Syndrome (aHUS) | 4/29/2009 | Alexion Pharmaceuticals, Inc. |
| 10/14/2011 | Deferiprone | Ferriprox | Treatment of patients with transfusional iron overload due to thalassemia syndromes | 12/12/2001 | ApoPharma, Inc. |
| 10/21/2011 | Clobazam | Onfi | Adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome inpatients | 12/18/2007 | Lundbeck, Inc. |

| Marketing Approval | Generic Name | Trade Name | Designation (may be abbreviated) | Orphan Designation | Company |
|---|---|---|---|---|---|
| 11/16/2011 | Ruxolitinib phosphate | Jakafi | Treatment of patients with intermediate or high-risk myelofibrosis | 9/5/2008 | Incyte Corporation |
| 11/18/2011 | Erwinia L-asparaginase | Erwinase | Treatment of patients with acute lymphoblastic leukemia | 7/30/1986 | Jazz Pharmaceuticals, Inc. |
| 1/17/2012 | Glucarpidase | Voraxaze | Treatment of toxic plasma methotrexate concentrations | 8/19/2003 | BTG International Inc. |
| 1/31/2012 | Ivacaftor | Kalydeco | Treatment of cystic fibrosis (CF) in patients who have a G551D mutation in the CFTR gene | 12/20/2006 | Vertex Pharmaceuticals, Inc. |
| 2/7/2012 | Mitomycin-C | Mitosol | An adjunct to ab externo glaucoma surgery. | 1/8/2008 | Mobius Therapeutics, LLC |
| 2/17/2012 | Mifepristone | Korlym | To control hyperglycemia secondary to hypercortisolism in patients with endogenous Cushing's syndrome | 7/5/2007 | Corcept Therapeutics, Inc. |
| 4/26/2012 | Pazopanib | Votrient | Advanced soft tissue sarcoma (STS) patients who have received prior chemotherapy | 10/20/2009 | GlaxoSmithKline |
| 5/1/2012 | Taliglucerase alfa | Elelyso For Injection | Use as long-term enzyme replacement therapy in patients with Type 1 Gaucher disease | 9/3/2009 | Pfizer, Inc. |
| 6/6/2012 | Gabapentin enacarbil | Horizant | Management of postherpetic neuralgia in adults | 6/7/2011 | XenoPort, Inc. |
| 6/13/2012 | Difluprednate | Durezol | Treatment of endogenous anterior uveitis | 9/30/2008 | Alcon Pharmaceuticals. Ltd. |
| 6/22/2012 | Immune globulin infusion (human) | Gammagard Liquid | Improve muscle strength and disability in adult patients with Multifocal Motor Neuropathy (MMN) | 7/20/2006 | Baxter Healthcare Corporation |
| 7/20/2012 | Carfilzomib | Kyprolis | Treatment of patients with multiple myeloma | 1/18/2008 | Onyx Therapeutics, Inc. |
| 8/9/2012 | VinCRIStine sulfate LIPOSOME injection | Marqibo | Treatment of patients with Philadelphia chromosome-negative (Ph-) acute lymphoblastic leukemia (ALL) | 1/8/2007 | Talon Therapeutics, Inc. |
| 8/13/2012 | Technetium Tc99m sulfur colloid injection, lyophilized | Technetium Tc99m Sulfur Colloi | Localization of lymph nodes draining a primary tumor in patients with melanoma | 3/17/2009 | Pharmalucence, Inc. |
| 9/4/2012 | Bosutinib | Bosulif | Treatment of Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) | 2/24/2009 | Wyeth Pharmaceuticals, Inc. |
| 10/2/2012 | Cysteamine hydrochloride | Cystaran | Treatment of corneal cystine crystal accumulation in patients with cystinosis | 8/19/1997 | Sigma-Tau Pharmaceuticals, Inc. |

| Marketing Approval | Generic Name | Trade Name | Designation (may be abbreviated) | Orphan Designation | Company |
|---|---|---|---|---|---|
| 10/26/2012 | Omacetaxine mepesuccinate | Synribo | Treatment of chronic or accelerated phase chronic myeloid leukemia (CML) | 3/10/2006 | IVAX International GmbH |
| 11/29/2012 | Cabozantinib | Cometriq | Treatment of progressive, metastatic medullary thyroid cancer (MTC) | 11/29/2010 | Exelixis, Inc. |
| 12/14/2012 | Pasireotide | Signifor | Treatment of adult patients with Cushing's disease | 7/24/2009 | Novartis Pharmaceuticals Corporation |
| 12/14/2012 | Ponatinib | Iclusig | Treatment of adult patients with chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) | 11/20/2009 | ARIAD Pharmaceuticals Inc. |
| 12/14/2012 | Raxibacumab | Abthraxtm | Treatment of inhalation anthrax due to Bacillus anthracis | 11/12/2003 | Human Genome Sciences, Inc. |
| 12/20/2012 | Varicella Zoster Immune Globulin (Human) | Varizig | Post exposure prophylaxis of varicella in high risk individuals to reduce the severity of varicella | 11/7/2006 | Cangene bioPharma, Inc. |
| 12/21/2012 | Lomitapide | Juxtapid | Adjunct to lipid-lowering treatments for homozygous familial hypercholesterolemia (HoFH) | 10/23/2007 | Aegerion Pharmaceuticals, Inc. |
| 12/21/2012 | Anakinra | Kineret | Treatment of neonatal-onset multisystem inflammatory disease (NOMID) | 8/19/2010 | Swedish Orphan Biovitrum AB (publ) |
| 12/21/2012 | Teduglutide [rDNA origin] | Gattex | Treatment of adult patients with short bowel syndrome (SBS) | 6/9/2000 | NPS Pharmaceuticals, Inc. |
| 12/28/2012 | Bedaquiline; (1R,2S) 6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-(1-naphthyl)-beta-phenyl-3-quinolineethanol | Sirturo | Part of combination therapy in adults with pulmonary multi-drug resistant tuberculosis (MDR-TB) | 1/10/2005 | Janssen Research & Development, LLC |
| 1/29/2013 | Mipomersen | Kynamro | Reduce cholesterol in patients with homozygous familial hypercholesterolemia (HoFH) | 5/23/2006 | Genzyme Corporation |
| 2/1/2013 | Glycerol phenylbutyrate | Ravicti | Use as an adjunctive therapy for chronic management of urea cycle disorders (UCDs) | 4/27/2009 | Hyperion Therapeutics, Inc. |
| 2/8/2013 | Pomalidomide | Pomalyst | Treatment of patients with multiple myeloma | 1/15/2003 | Celgene Corporation |
| 2/25/2013 | Regorafenib | Stivarga | Treatment of locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) | 1/12/2011 | Bayer HealthCare Pharmaceuticals, Inc. |

| Marketing Approval | Generic Name | Trade Name | Designation (may be abbreviated) | Orphan Designation | Company |
|---|---|---|---|---|---|
| 3/8/2013 | Immune globulin intraveous (human) | Gammaplex | Treatment of idiopathic thrombocytopenic purpura | 4/29/2011 | Bio Products Laboratory |
| 3/22/2013 | Botulism antitoxin heptavalent (A, B, C, D, E, F, G) (Equine) | -- | Treatment of symptomatic botulism following documented or suspected exposure to botulinum neurotoxin serotypes A, B, C, D, E, F, or G | 6/29/2011 | Cangene Corporation |
| 4/29/2013 | Tocilizumab | Actemra | Treatment of active polyarticular juvenile idiopathic arthritis in patients aged 2 to 16 years | 7/31/2012 | Genentech, Inc. |
| 4/29/2013 | Prothrombin complex concentrate (human) | Kcentra | Urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist therapy (VKA, e.g., warfarin) in adult patients | 12/27/2012 | CSL Behring |
| 4/30/2013 | Cysteamine enteric coated | Procysbi | Management of nephropathic cystinosis in adults and children ages 6 years and older | 10/24/2006 | Raptor Therapeutics, Inc. |
| 5/9/2013 | Canakinumab | Ilaris | Treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 to 16 years | 9/30/2008 | Novartis Pharmaceuticals Corporation |
| 5/10/2013 | Nimodipine | Nymalize | Treatment of subarachnoid hemorrhage (SAH) from ruptured intracranial berry aneurysms | 9/16/2011 | Arbor Pharmaceuticals, Inc. |
| 5/17/2013 | Japanese encephalitis vaccine, inactivated, adsorbed | Ixiaro | To include infants, children, and adolescents for active immunization for the prevention of disease caused by Japanese encephalitis virus | 9/25/2012 | Intercell AG |
| 5/29/2013 | Trametinib | Mekinist | Treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations | 12/20/2010 | GlaxoSmithKline, LLC |
| 5/29/2013 | Dabrafenib | Tafinlar | Treatment of unresectable or metastatic melanoma with BRAF V600E mutation | 1/12/2011 | GlaxoSmithKline, LLC |
| 6/5/2013 | Lenalidomide | Revlimid | Treatment of mantle cell lymphoma that has relapsed or progressed | 4/27/2009 | Celgene Corporation |
| 6/13/2013 | Denosumab | Xgeva | Treatment of adults and skeletally mature adolescents with giant cell tumor of bone | 12/20/2010 | Amgen, Inc. |
| 6/26/2013 | Coagulation factor IX (recombinant) | Rixubis | Adults with Hemophilia B for routine prophylaxis to prevent or reduce the frequency of bleeding episodes | 10/31/2012 | Baxter Healthcare Corporation |
| 7/12/2013 | Afatinib | Gilotrif | First-line treatment of patients with metastatic non-small cell lung cancer (NSCLS) | 12/3/2012 | Boehringer Ingelheim Pharmaceuticals, Inc. |

| Marketing Approval | Generic Name | Trade Name | Designation (may be abbreviated) | Orphan Designation | Company |
|---|---|---|---|---|---|
| 8/13/2013 | Eenalapril maleate (powder for oral solution) | Epaned | Treatment of hypertension in adults and children older than one month, to lower blood pressure | 1/30/2013 | Silvergate Pharmaceuticals, Inc. |
| 8/23/2013 | Meclorethamine | Valchlor | Topical treatment of Stage 1A and 1B mycosis fungoides-type cutaneous T-cell lymphoma | 8/17/2004 | Actelion Pharmaceuticals Ltd. |
| 9/6/2013 | Paclitaxel protein-bound particles | Abraxane | Treatment of metastatic adenocarcinoma of the pancreas | 9/3/2009 | Abraxis BioScience, LLC |
| 10/8/2013 | Riociguat | Adempas | Treatment of adults with pulmonary arterial hypertension (PAH) WHO Group 1 | 9/19/2013 | Bayer HealthCare Pharmaceuticals, Inc. |
| 10/8/2013 | Riociguat | Adempas | Treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) WHO Group 4 | 9/19/2013 | Bayer HealthCare Pharmaceuticals, Inc. |
| 10/18/2013 | Macitentan | Opsumit | Treatment of pulmonary arterial hypertension (PAH, WHO Group 1) | 9/3/2009 | Actelion Pharmaceuticals Ltd |
| 11/1/2013 | Obinutuzumab | Gazyva | Treatment of patients with previously untreated chronic lymphocytic leukemia | 12/17/2012 | Genentech, Inc. |
| 11/13/2013 | Ibrutinib | Imbruvica | Treatment of patients with mantle cell lymphoma (MCL) | 12/3/2012 | Pharmacyclics, Inc. |
| 11/22/2013 | Sorafenib | Nexavar | Treatment of patients with locally recurrent or metastatic, progressive, differentiated thyroid carcinoma (DCT) | 12/12/2011 | Bayer HealthCare Pharmaceuticals, Inc. |
| 12/6/2013 | Collagenase clostridium histolyticum | Xiaflex | Treatment of adult men with Peyronie's disease | 3/12/1996 | Auxilium Pharmaceuticals, Inc. |
| 12/13/2013 | Prothrombin complex concentrate (human) | Kcentra | Urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist therapy (VKA, e.g., warfarin) in adult patients | 12/27/2012 | CSL Behring |
| 12/16/2013 | Anti-inhibitor coagulant complex | Feiba | Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in hemophilia A and B patients with inhibitors | 4/12/2013 | Baxter Healthcare Corporation |
| 12/23/2013 | Coagulation factor XIII A-subunit (recombinant) | Tretten | Routine prophylaxis of bleeding in patients with congenital Factor XIII A-subunit deficiency | 11/6/2003 | Novo Nordisk, Inc. |
| 1/8/2014 | Trametinib | Mekinist | Combination treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations | 9/20/2012 | GlaxoSmithKline, LLC |

| Marketing Approval | Generic Name | Trade Name | Designation (may be abbreviated) | Orphan Designation | Company |
|---|---|---|---|---|---|
| 1/9/2014 | Dabrafenib | Tafinlar | Combination treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations | 9/20/2012 | GlaxoSmithKline, LLC |
| 1/31/2014 | Tasimelteon | Hetlioz | Treatment of non-24-hour sleep-wake disorder | 1/19/2010 | Vanda Pharmaceuticals, Inc. |
| 2/12/2014 | Ibrutinib | Imbruvica | Treatment of patients with chronic lymphocytic leukemia (CLL) | 4/6/2012 | Pharmacyclics, Inc. |
| 2/14/2014 | elosulfase alfa | Vimizim | Patients with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome) | 5/15/2009 | BioMarin Pharmaceutical Inc. |
| 2/18/2014 | Droxidopa | Northera | Treatment of adult patients with symptomatic neurogenic orthostatic hypotension | 1/17/2007 | Chelsea Therapeutics, Inc. |
| 2/24/2014 | Metreleptin | Myalept | Treat complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy | 8/22/2001 | Amylin Pharmaceuticals, LLC |
| 3/14/2014 | Propranolol | Hemangeol | Treatment of proliferating infantile hemangioma requiring systemic therapy | 9/5/2008 | Pierre Fabre Dermatologie |
| 3/19/2014 | Miltefosine | Impavido | Treatment of visceral leishmaniasis, cutaneous leishmaniasis, and mucosal leishmaniasis | 10/10/2006 | Paladin Therapeutics, Inc. |

# 2. OVERVIEW OF ASIA

## 2.1 THE ASIAN ECONOMY

Asia is the largest and most populated continent and had the most rapid economic growth in the world for several decades (see Table 2 below). Over the past few years, the Asian economy has been growing steadily at 6-8% per year and is expected to continue this upward trend. Asia's economic expansion has helped reduce poverty throughout the region and increase living standards.

**Table 2: Asian Demographics**

| Country | Population (millions) (2013) | Population Growth (2013) | GDP (PPP) (2012) | GDP Real Growth Rate (2013) | Per capita GDP (PPP) (2012) | Life Expectancy (Years) (2013) |
|---|---|---|---|---|---|---|
| China | 1,351 | 0.46% | $12.2 trillion | 7.7% | $9,100 | 75 |
| Hong Kong | 7 | 0.39% | $366 billion | 3% | $50,900 | 82 |
| India | 1,221 | 1.28% | $4.7 trillion | 3.8% | $3,800 | 67 |
| Indonesia | 251 | 0.99% | $1.2 trillion | 5.3% | $4,900 | 72 |
| Japan | 127 | -0.1% | $4.6 trillion | 2% | $35,900 | 84 |
| Korea | 49 | 0.18% | $1.6 trillion | 3% | $31,900 | 80 |
| Malaysia | 30 | 1.51% | $495 billion | 4.7% | $16,800 | 74 |
| Philippines | 106 | 1.84% | $420 billion | 6.8% | $4,400 | 72 |
| Singapore | 5 | 1.96% | $323 billion | 3.5% | $60,800 | 84 |
| Taiwan | 23 | 0.27% | $894 billion | 2.2% | $38,400 | 80 |
| Thailand | 67 | 0.52% | $645 billion | 3.1% | $9,500 | 74 |
| Vietnam | 92 | 1.03% | $336 billion | 5.3% | $3,800 | 73 |

*Source: CIA World Factbook, PBM estimates.*

## 2.2 THE PHARMACEUTICAL MARKETS IN ASIA

One industry which has greatly benefited from the Asian economic boom is the healthcare sector. With increased wealth and daily living standards, many Asian citizens are seeking improved healthcare. In response, a number of Asian governments have been making a conscious effort to improve their healthcare standards and regulations in order to meet the demands of their citizens.

In particular, the Asian pharmaceutical industry has been expanding very quickly due to the aging populations and resulting demand for healthcare. Currently, the global pharmaceutical industry is worth almost $1 trillion, with the Asian countries contributing nearly one-fourth of the market share. The markets in Japan and China alone were estimated to be close to $170 billion in 2013 (see Table 3). The Asian pharmaceutical

industry is expected to grow by more than 10% per year. This is faster than the average annual pharmaceutical growth of about 3-4% in more developed Western countries.

**Table 3: Size of the Asian Pharmaceutical Markets (2013)**

| Country | Pharmaceutical Market Size (US$) |
|---|---|
| China | $65 billion |
| Hong Kong | $7 billion |
| India | $20 billion |
| Indonesia | $5.9 billion |
| Japan | $104 billion |
| Korea | $15 billion |
| Malaysia | $3.1 billion |
| Philippines | $3.4 billion |
| Singapore | $840 million |
| Taiwan | $5.4 billion |
| Thailand | $4.8 billion |
| Vietnam | $3.2 billion |

*All data collected by Pacific Bridge Medical*

# 3. ORPHAN DRUGS IN ASIA

## 3.1 DO ORPHAN DRUGS HAVE POTENTIAL IN ASIA?

Asia's population is about 4.3 billion, making up close to two-thirds of the world's 7.2 billion inhabitants. As mentioned in the introduction of this report, about one in ten people in the world have a rare disease. Therefore, Asia has huge long-term potential for orphan drug medications and treatments. Based on a recent market survey in Asia, the top three highest potential for the orphan drug market are oncology, genetic and autoimmune diseases. Other diseases with potential in the orphan drug market are endocrinology, cardiovascular, blood and lymphatic systems, as well as respiratory disorders.

While some Asian countries such as Japan, Taiwan, Korea, Hong Kong, and Singapore have highly advanced healthcare systems and well-trained doctors, other Asian countries, such as China and Thailand, are still striving to improve their system. Japan has one of the largest and most technologically-advanced healthcare systems in the world, comparable to that of the US or EU. Each Asian country's healthcare system differs greatly in structure and quality, so the potential for an orphan drug's success will also vary. Furthermore, issues such as rare disease awareness, health insurance coverage, and prosperity will also play a strong role in the success or failure of an orphan drug in each Asian country. Impoverished sufferers of rare diseases will generally have little access to the appropriate treatments.

## 3.2 WHY SEEK ORPHAN DRUG STATUS?

The drug registration and approval process can be a lengthy and complicated ordeal in any country. Depending on the amount of clinical data required, the process can take many years to complete. While not all countries offer a registration process specifically for orphan drugs, it is generally best to use this procedure where available. Sometimes, the orphan drug registration process can be expedited and treated as a priority case. For example, the following is a list of potential benefits offered by the US FDA to applicants who are granted orphan drug designation:

- Up to a 50% tax credit on research and development costs
- Fast-track product registration process
- Exemption from user fee (unless the drug also has a non-orphan indication)
- Marketing exclusivity for 7 years after the product approval is granted
- In some cases, availability of drug to patients *prior* to product approval (patient named basis)
- Some grants for clinical research (currently $14 million per year is allocated, $200,000 for Phase 1 trials or $400,000 for Phase 2 and 3 trials)

# 4. ISSUES TO CONSIDER PRIOR TO ORPHAN DRUG REGISTRATION

## 4.1 INTRODUCTION

As mentioned in the introduction, the development and registration of a drug can cost up to $100 million and take over a decade to complete. Moreover, since the registration of an orphan drug generally requires that additional qualifications are met (limited number of patients in the country, etc.), there are a number of issues one should consider prior to beginning the orphan drug registration process.

## 4.2 ARE TREATMENT OPTIONS ALREADY AVAILABLE IN THE COUNTRY?

If a pharmaceutical company has developed a drug to treat a disease or condition for which no treatment is currently available, obtaining orphan drug status should be a feasible undertaking. In this particular case, the patient number limitation may even be waived since patients currently have no treatment options available to them.

Orphan drug companies should also keep in mind that the absence of a treatment in a country can imply that the awareness of the disease among doctors, hospitals and patients is low. Therefore, it is important to determine the number of currently diagnosed patients and the accuracy of this number. Unless an orphan drug company has doctors, hospitals or medical organizations that will support and increase awareness of the disease, market penetration (and potential sales) could be weak.

In cases where there is some awareness of the disease in the country, it is crucial to seek out and garner the support of Key Opinion Leaders (KOLs). Especially in relatively small countries like Korea, Taiwan, and Malaysia there may only be a handful of doctors in the country who specialize in the disease. Therefore, their support will be critical both to regulators considering the drug and to the success of the drug's marketing. Your KOL outreach may include, where appropriate, having the doctors try the drug on their patients on a personal import basis. Doctors enjoy a very high level of social regard in Asia. This means that satisfied doctors will be particularly persuasive to Asian regulators, especially if they are already known as experts in the field.

If a competing product is already available in the country, it is still possible to register a drug as an orphan product and receive approval. However, the new drug will need to be superior to the product currently on the market; data demonstrating this superiority will play a crucial role in the orphan drug designation process.

## 4.3 IS YOUR DRUG SUPERIOR TO THOSE ALREADY ON THE MARKET?

If a competing product is already present in the market, a "product comparison" will be necessary along with the product dossier in order to show superiority over the competitor.

The following is a list of supportive factors for orphan drug designation:

- Better efficacy
- Lower drug cost
- Reduction in the dosage frequency
- Different method of administration (important consideration if disease/condition is common among children – liquid vs. tablet vs. injection)
- Reduction in side-effects
- Product availability (Is your competitor able to produce adequate quantities of the drug to meet its demands?)
- Better reputation (Has your competitor had any significant problems with adverse effects, etc.?)

## 4.4 CONCLUSION

The issues discussed in this section can assist a pharmaceutical company in evaluating their potential orphan drug and the Asian market they plan to enter. The actual registration process for each Asian country is outlined in the following sections of this report. Some Asian countries have an application process specifically for orphan drugs, while other countries do not. Nevertheless, the registration option(s) available in each country will be discussed, as well as application strategies, reimbursement and other important issues.

# 5. JAPAN

## 5.1 INTRODUCTION

Japanese healthcare standards are among the highest in the world. The Japanese spend an average of $450 billion on healthcare per year. Even though this number is less than the $2.8 trillion spent by the US every year, Japan's demand for better and safer healthcare is rising quickly as the country's elderly population grows. Subsequently, the Ministry of Health, Labor and Welfare (MHLW) has become more aware of the need to improve the regulatory and safety environment for pharmaceuticals.

## 5.2 MINISTRY OF HEALTH, LABOR AND WELFARE

The MHLW is responsible for ensuring good living standards among Japanese people and for promoting the development of new health programs and innovations to improve people's lives. Social security, public health, working conditions and social welfare are all regulated by the MHLW. Additionally, the MHLW oversees all health programs in Japan, including health insurance, food, drugs and medical devices. The Pharmaceutical and Food Safety Bureau within the MHLW is responsible for pharmaceutical regulatory policymaking.

## 5.3 PHARMACEUTICALS AND MEDICAL DEVICES AGENCY

Over the past few years, the MHLW has been undergoing major restructuring, altering the regulatory requirements and procedures for registering and marketing pharmaceuticals and medical devices in Japan. In April 2004, the Pharmaceuticals and Medical Devices Agency (PMDA) was formed by merging three already-existing organizations: (1) the Pharmaceuticals and Medical Devices Evaluation Center (PMDEC), (2) the Organization of Pharmaceutical Safety and Research (OPSR) and (3) the Japan Association for the Advancement of Medical Equipment (JAAME). The PMDA conducts registration of pharmaceutical and medical devices for marketing, according to MHLW policies.

## 5.4 ORPHAN DRUGS IN JAPAN

### 5.4.1 Introduction

The Orphan Drug Development Program in Japan was initiated by the MHLW in 1993 to support the development of life-saving, but generally non-profitable, drugs. By January 2014, the MHLW had designated 327 products as orphan drugs. Of these, 203 have been approved for marketing (see Table 4 below).

| Table 4: Orphan Drug Application Statistics in Japan* | | | | |
|---|---|---|---|---|
| **Year** | **Designations** | **Approvals** | **Under Development** | **Cancellations** |
| 1993 | 40 | 33 | 0 | 7 |
| 1994 | 29 | 18 | 1 | 11 |
| 1995 | 11 | 7 | 0 | 5 |
| 1996 | 28 | 22 | 1 | 6 |
| 1997 | 4 | 2 | 1 | 1 |
| 1998 | 13 | 9 | 0 | 4 |
| 1999 | 14 | 12 | 1 | 2 |
| 2000 | 9 | 8 | 1 | 0 |
| 2001 | 8 | 4 | 0 | 4 |
| 2002 | 5 | 5 | 0 | 0 |
| 2003 | 7 | 6 | 1 | 0 |
| 2004 | 11 | 9 | 1 | 1 |
| 2005 | 3 | 2 | 1 | 0 |
| 2006 | 17 | 14 | 2 | 1 |
| 2007 | 8 | 7 | 1 | 0 |
| 2008 | 16 | 8 | 6 | 2 |
| 2009 | 4 | 3 | 1 | 0 |
| 2010 | 15 | 10 | 5 | 0 |
| 2011 | 27 | 16 | 11 | 0 |
| 2012 | 31 | 6 | 24 | 1 |
| 2013 | 27 | 2 | 25 | 0 |
| **TOTALS** | **267** | **203** | **83** | **45** |

**As of February 2014*
*Source: National Institute of Biomedical Innovation (NIBIO), Japan*

The Orphan Drug Development Program has enabled numerous orphan drug developers to enter the Japanese market, including a number of small- and mid-size foreign companies. Of orphan drug designations to date, close to half of the drug developers are non-Japanese companies, demonstrating the success of foreign companies in Japan at receiving orphan drug approvals. The majority of the orphan drugs approved in Japan are used for treating infectious diseases, hematological diseases, neuromuscular diseases, and diseases common in children or infants.

### 5.4.2 Orphan Drug Definition

A drug must meet the following three conditions in order to be considered for orphan drug designation:

1. The drug is used to treat a rare disease or condition affecting less than 50,000 persons in Japan -- with a maximum of 4 persons per 10,000 (.05% of the Japanese population). It is important to note that if the number of patients affected by the disease is approaching 50,000 (i.e. 45,000), the MHLW may decide not to grant the orphan drug designation.
2. The drug treats a disease or condition for which there are no other drugs/treatments available in Japan or the proposed drug is clinically superior to drugs already available on the Japanese market (in terms of efficacy and safety).
3. The applicant should have a clear product development plan and scientific rationale so that the eventual marketing of the drug in Japan is more likely.

### 5.4.3 Benefits of Orphan Drug Designation

Drug companies that are granted orphan drug designation are eligible to receive the following benefits.

1. The MHLW has a consultation service specifically for orphan drug designation applicants and the service fee may be reduced; typically the first meeting is free. The consultation services for "regular" drugs can cost as much as $20,000 for a typical product.

2. In the majority of orphan drug designations, fewer clinical trials in Japan are required for product approval than are required in the West.

3. The applicant may receive financial aid for the collection of supporting data, such as for conducting clinical trials, bridging studies, etc. Specifically, the applicant may receive as much as 50% of the cost of clinical development costs in financial aid, as well as tax exemptions of up to 12% of drug development/research costs and up to 14% of corporate taxes. Financial aid is awarded by the National Institute of Biomedical Innovation (NIBIO), which is part of the Japanese equivalent of the US's National Institutes of Health (NIH). NIBIO also currently arranges and schedules the free MHLW consultations described above.

4. The application will be placed on a fast-track approval process, which generally proceeds much more smoothly than that of "regular" drugs. In theory, the fast-track approval process takes 10 months while the approval for "regular" drugs takes 12 months.

5. The applicant will be granted a 10-year period of marketing exclusivity, wherein no generic versions of their product may be placed on the market by the MHLW.

However, 10 years is the *maximum* period of marketing exclusivity; it is possible that the MHLW could reduce this period, on a case-by-case basis.

6. Product renewal for orphan drugs is every 10 years, versus every 4 to 6 years for other drugs.

7. The PMDA's review and validation fees are significantly reduced for orphan drugs as compared to regular drugs. Although the exact fees vary depending on application type, total fees typically go down by about 25%.

### 5.4.4 Applying for Orphan Drug Designation

#### *5.4.4.1 Overview*

The MHLW currently has one person who handles orphan drug designation applications: Mr. Shimoaraiso. Mr. Shimoaraiso will explain the application process, including what information should be included with the application, which documents need to be translated, and whether any documents need to be revised. An applicant should be prepared for frequent correspondence with Mr. Shimoaraiso and the MHLW when developing their regulatory strategy.

#### *5.4.4.2 Japan's Orphan Drug Designation Application Requirements*

| | Required Documents and Information | Details |
|---|---|---|
| **Form No. 107-1** | | |
| 1 | Application form:<br>1 official, 2 duplicate | a. Product name<br>b. Ingredients<br>c. Manufacturing process<br>d. Dosage and administration<br>e. Possible side-effects<br>f. Supporting data as a life-saving drug<br>g. Company name and address<br>h. Marketing Authorization Holder information<br>i. Date |
| **Attached Data** | | |
| 2 | Data on number of patients | Statistical papers, interviews with Japanese doctors, medical associations, etc. |
| 3 | Necessity of the drug | a. Causes and symptoms of rare disease/condition the drug would be used to treat.<br>b. Proposed indication(s).<br>c. Reasons why the drug (therapy) is needed.<br>d. List of similar products/treatments available in Japan.<br>e. Explanation of why the drug is clinically superior to drugs already available in Japan (if applicable). |

| | | |
|---|---|---|
| **4** | Scientific Rationale | Discussion of the scientific rationale supporting the use of the drug for the rare disease/condition, including data from non-clinical laboratory studies, clinical investigations, etc. |
| **5** | Development Plan | a. Clinical trial plan and estimated timeframe.<br>b. Estimated cost of clinical trials.<br>c. Number of patients needed for the trials.<br>d. If any doctors in Japan already have experience using the drug, the applicant should ask the doctors to develop a clinical report as supportive information. |
| **6** | If product is already approved in another country, status of overseas approval. | a. US FDA product summary and basis of approval.<br>b. US FDA NDA approval number and date.<br>c. EU product summary and basis of approval.<br>d. EMEA registration number and date.<br>e. Any clinical data for Asian patients.<br>f. Any marketing information in foreign countries.<br>g. Any adverse event reports in post-marketing settings such as Periodic Safety Update Reports (PSUR). |

**Orphan Drug Designation Application Form (Form No. 107-1)**
(Submit to the Evaluation and Licensing Division of the Pharmaceutical and Food Safety Bureau (PFSB) of the MHLW)

**Orphan Drug Designation Application Form (Form No. 107-1)**

| | |
|---|---|
| Name | |
| Ingredients and contents or nature | |
| Manufacturing method | |
| Anticipated dosage and administration | |
| Anticipated indications | |
| Reason to judge that the practical value is particularly high | |
| Remarks | |

We hereby apply for orphan drug designation shown above.

Date

Address
Name (Seal)

To: Minister of Health, Labor and Welfare

*Source: Drug Approval and Licensing Procedures in Japan 2008 (Jiho, Inc.)*
*Notes*
1. *Use the A4 format (JIS).*
2. *The applicant must submit one original copy and two duplicate copies.*

3. *Complete in clearly legible block letters using India ink or ink.*

#### *5.4.4.3 What if there are already competitive products on the market in Japan?*

There is no regulation preventing more than one orphan drug designation and approval for the same indication in Japan. For instance, if a product is already on the market in Japan and designated as an orphan drug for the treatment of Disease A, this *does not* prevent another drug from receiving orphan drug designation and entering the Japanese market to also treat Disease A. However, the MHLW will almost always be reluctant to support two drugs with the same indication, so the applicant of the second drug should be able to show significant superiority to the drug already on the market.

#### *5.4.4.4 Supportive Data*

The following types of data will be supportive in showing that the disease/condition treated by the orphan drug affects less than 50,000 persons in Japan:

- Statistical data from an "official" source (government health authority, medical organization, etc.) showing the estimated number of patients with the disease. Note: there are research groups organized by the MHLW which often issue reports with patient data.
- If statistical reports are unavailable, the applicant can interview Japanese doctors, contact medical associations or hire an investigational consultant to determine the estimated number of patients in Japan.
- There is statistical data on patient numbers located on the MHLW website, but it is available in Japanese only.

The MHLW determines the amount of clinical data required for an orphan drug application and approval on a case-by-case basis. The following types of data are accepted by the MHLW:

- Any Japanese clinical data.
- Clinical studies done under the same conditions (same dosage, etc.) and for the same indication as the current orphan drug application. Foreign data under the same conditions may also be supportive.
- Data from off-label use in Japan.
- Any bridging or comparative studies done under the same conditions (same dosage, etc.) as the current indication that demonstrate the safety and efficacy of the drug.
- Other important data such as the raw data from clinical studies compiled in the NDA package, Clinical Safety Data Management, etc.

Of course, data gathered in Japan is most valuable. Generally, foreign or Asian (non-Japanese) data is considered more as reference data by the MHLW, though recently there have been more cases of foreign data being accepted. Japanese data is considered most supportive in terms of getting the product approved.

### 5.4.5 Networking for Product Support

In Japan, as in other Asian countries, it is particularly important to identify doctors or Key Opinion Leaders who may be interested in your orphan drug. It is best to target doctors focused on the specific disease/condition your drug treats in order to obtain the strongest support for your product.

First, compile a list of potential doctors or Key Opinion Leaders who may be interested in your product. Introduce your orphan drug to these doctors and try to establish good working relationships with them. If a doctor obtains favorable results from your product, they may be willing to write a letter of recommendation to support your orphan drug application. Additionally, any case studies that these doctors can provide will also be valuable, though published papers are more persuasive in the eyes of the MHLW.

Second, identify any related Japanese medical associations that may be interested in your drug. A representative from the association may also be willing to provide a letter of recommendation for your application if he/she sees the drug as beneficial. Keep in mind that obtaining support from a medical organization may require a small monetary donation ($5,000 - $20,000).

*Please note: Japan is a very political, bureaucratic and conservative country. Doctors hold a very high status in Japanese society and are treated with the utmost authority. Therefore, it can be very difficult to make appointments with doctors, especially if one is requesting a face-to-face meeting. Very careful research by a professional consultant may be required to appropriately network with key doctors and obtain the necessary support.*

### 5.4.6 MHLW Consultation Service – Orphan Drugs

The MHLW provides a special consultation service for companies applying for orphan drug designation. The typical procedure for the consultation process is as follows.

The applicant should submit a consultation request form (see next page) to the designation administrator (person in charge of orphan drug designations) at the Evaluation and Licensing Division of the Pharmaceutical and Food Safety Bureau (PFSB) of the MHLW. The form can be sent by mail or fax. If the request is approved, the designation administrator will notify the applicant of his or her consultation date by phone or fax.

The consultation itself takes around 30 minutes with a "sufficient" number of people appropriate to the applicant's level of need. The applicant should submit five copies of the draft designation application (see next page), with other information attached, such as scientific evidence, research, literature, a list of references etc., to the Evaluation and Licensing Division at least one week prior to the consultation date.

Attachment Form 1

**Orphan Drug etc. Designation Consultation Form**

To: Person in charge of orphan drug designation, Pharmaceutical and Safety Bureau, Minister of Health, Labor and Welfare

| | |
|---|---|
| Company name | Name of consulter (Name of participant and department) |
| Phone number/Fax number | Preferred date of consultation<br>First choice:<br>Second choice:<br>Third choice: |
| Name of substance to be designated | |
| Anticipated indications | |
| Matter to consult | |

*Source: Drug Approval and Licensing Procedures in Japan 2008 (Jiho, Inc.)*
*Notes:*
1. *The information must be specific and concise*
2. *Use the A4 format (JIS).*

*The preferred consultation day may not be available*

Attachment Form 2

**Outline of Orphan Drug etc.**

| | |
|---|---|
| Name | |
| Anticipated indications | |
| Name of applicant | |
| Target disease | |
| Indications of this drug for target disease | |

*Source: Drug Approval and Licensing Procedures in Japan 2008 (Jiho, Inc.)*
*Notes:*
1. *Use the A4 format (JIS).*
2. *The applicant may include attachments if more space is needed.*

### 5.4.7 MHLW Consultation Service -- General Information

The MHLW also provides sessions for companies applying for other drug designations.

First, the future applicant should send NIBIO an inquiry via fax, including a summary of their current situation, what the company hopes to accomplish and any general questions. (If this is done on a no-name basis, there may be no response.) Approximately 7-10 days later, NIBIO will respond to the inquiry via fax or email. Depending on how the MHLW interprets the questions, either a face-to-face meeting will be held or the MHLW will continue the communication by fax or email. Sometimes, the company will be able to obtain their answer through these communications without meeting. It is possible that the MHLW will request additional information before meeting face-to-face.

Based on experience, there is usually a three to four-month wait between applying for a meeting and holding the meeting. This wait may decrease as the MHLW hires more staff.

The first in-person consultation meeting is normally free; future meetings usually require a fee. In the first meeting, the MHLW will usually review the situation and give their general opinion on how the company can proceed. In the next meeting, the MHLW will provide more details on the situation and may give a rough estimate of the number of clinical trials required for the drug designation (assuming the MHLW is considering granting the designation). Around the time of the third meeting, the company should be able to provide information on how they plan to proceed with the clinical trials. For instance, if the MHLW states during the second consultation meeting that 10-15 trials will be necessary, the applicant should present a plan for conducting these trials.

According to PMDA statistics, there were 355 consultation sessions held for pharmaceutical clinical trials in the 2010 fiscal year (ending March 31, 2011). These consultation sessions usually last 1.5-2 hours.

It should be noted that although the first consultation sessions arranged through NIBIO specifically for orphan drugs are free, that does *not* mean that all PMDA consultation sessions are free for orphan drugs. In fact, only *some* of the other types of PMDA consultation sessions offer reduced fees for orphan drugs. The following other types of sessions are available for general drugs (see Table 5 below):

**Table 5: PMDA Consultation Sessions (Drugs)**

| *Session topic / phase* | *Fee (USD approx.)* | |
|---|---|---|
| | *Non-orphan* | *Orphan* |
| General procedures | $1,396 | |
| Bioequivalence | $5,552 | |
| Safety | $17,802 | |
| Quality | $14,762 | |
| Prior to start of Phase I trial | $42,527 | $31,817 |
| Prior to start of Phase IIa trial | $16,499 | $12,208 |
| Prior to start of Phase IIb trial | $30,242 | $22,711 |
| After completion of Phase II trial | $60,032 | $45,095 |
| Product application | $60,031 | $45,068 |
| Planning for clinical trial for reevaluation / reexamination | $33,160 | |
| After completion of clinical trial for reevaluation / reexamination | $33,148 | |
| Additional consulting | $26,719 | $20,077 |
| GLP/GCP compliance | $28,716 | |

** Fees as of April 1, 2014*
** 1 USD = 103 JPY*

### 5.4.7 Orphan Drug Designation (ODD) -- Application Review

After a thorough consultation, the Evaluation and Licensing Division will hold hearings as needed to verify the content of the draft designation. Then, the orphan drug designation application is officially filed. The designation must be deemed permissible by two agencies: First, the PMDA, then the first or second committee on drugs of the Council on Drugs and Food Sanitation (CDFS). After approval by both groups, the drug is designated and a certificate will be sent to the applicant. The MHLW will also post a ministerial notification of the new designation in the government newspaper, including the ingredient, anticipated drug name, name and address of the applicant, and designation date.

### 5.4.8 PMDA Consultation Service

#### *5.4.8.1 Consultation Request and Preparation*

After the drug is designated as an orphan drug, the applicant is able to discuss the development of a Japanese clinical studies plan with the PMDA via a consultation service. To apply for the PMDA consultation, the orphan drug company first needs to fax or email NIBIO the information below:

1. Applicant's Information
    a. Company name
    b. Department

    c. Contact name and title
    d. Contact information (phone, fax and email)
2. Product Information
    a. Product name
    b. Orphan drug designation number
3. Consultation Information
    a. Suggested date of consultation meeting (several dates may be suggested)
    b. Topic to be discussed. Be specific; additional pages may be attached to help explain the situation more clearly

The fax/email request should be submitted in Japanese using an official NIBIO form. A sample of this form is provided in section 5.4.8.2 below. They may also be downloaded from http://www.nibio.go.jp/shinko/download/soudan_m.doc.

Generally, the consultation applicant will be contacted within a few business days of request submission to set the future date of the consultation. At that time, the company will need to confirm the date and time of the consultation as well as the number of people attending.

After the consultation date is set, the orphan drug company will need to submit the following information to the PMDA one day prior to the consultation session:

- Attendee list
    - Names
    - Department/title of each attendee
- Whether a translator will be necessary
- Requests for electronic equipment required for the company's presentation

*5.4.8.2 Consultation Request Form (Fax or Email)*

連絡票
【受信者】
医薬基盤研究所
研究振興部　希少疾病用医薬品等開発振興課　相談担当者　　宛
【発信者・連絡担当者】
【会社名】
【所属部署名】
【相談申込責任者又は担当者】
【連絡先】
TEL：
FAX：
Email：
【相談品目】
希少疾病用医薬品等の名称（指定 No. ）：
【相談事項】
【医薬品医療機器総合機構相談（事前相談、優先対面助言）】
実施予定日：
基盤研担当者同席の要否：

This form will be submitted to NIBIO when requesting PMDA consultative sessions by fax or email. The company is required to include the following information on the form:

- Date
- Name of sender / contact person
- Company name
- Title / Department
- Contact information - phone, fax, email
- Designated orphan drug name (product name)
- Orphan designation number
- Questions / topics the company wants to cover in the consultation (can include specific information and necessary attachments)
- Date the company wants to attend the consultation (suggest multiple choices)
- Whether the company wants a NIBIO official to attend the meeting as well as the PMDA official

#### *5.4.8.3 Consultation Meeting*

In the consultation meeting, the PMDA representative(s) will lead the meeting. The meeting should begin with the drug company presenting their orphan drug development plan, including the drug development completed to date. The company should describe their current development status and begin asking the PMDA specific questions. However, the PMDA will probably address only those topics and issues that the company listed on their consultation application form. The PMDA will typically avoid any additional topics.

#### *5.4.8.4 Consultation Minutes*

The PMDA requests that the drug company keep meeting minutes during the consultation session for future reference. The PMDA provides an example of the format and information required, as shown in section 5.4.8.5 below.

The example minutes form is only available in Japanese. However, the following is an English summary of the required information to be included:

- Date and location of meeting
- Attendee Information
    - Company name
    - Department/title
    - Contact name
    - PMDA representative(s) name and title
- Product Information
    - Product name
    - Orphan drug designation number and designation date
    - Targeted indication
- Discussion Summary
    - Summary of the current drug development situation
    - Questions presented by the company
    - Answers/advice/comments from the PMDA
- Future plans reflecting the meeting discussion

After the consultation meeting is held, the company will be responsible for providing a draft copy of the minutes to the PMDA representative who led the meeting. Both the PMDA and the company can discuss the minutes to ensure that the information is accurate. The confirmed information will become an official record. This "official record" can be used as supportive information in the new drug application dossier.

### *5.4.8.5 PMDA Consultation Minutes Form*

書式２：【相談記録】

希少疾病用医薬品等指定品目相談記録（参考例）
相談日時：平成○○年○月○日　○○：○○～○○：○○
場所：独立行政法人　医薬品医療機器総合機構　第○会議室
希少疾病用医薬品等の名称：
指定年月日：平成 ○○ 年 ○ 月 ○ 日　　指定番号：○○○
予定される効能又は効果：○○○○
出席者：独立行政法人　医薬品医療機器総合機構(以下「総合機構」と略す)
　　研究振興部　希少疾病用医薬品等開発振興課
　　課長　○○　○○、オーファン専門員　○○　○○
○○製薬㈱（以下「相談者」と略す）
　　○○部長○○　○○
　　薬事部○○　○○

本記録は、平成 年 月 日付で相談申込を行った××の相談について、相談者が作成して総合機構の確認を受けたものである。なお、本記録に示された判断等については、提出された資料等に基づき、相談実施時点における科学水準で行われたものであり、今後新たに得られる知見や科学の進歩等による、その妥当性についての解釈は、今後の相談において随時確認することとする。

１．これまでの経緯
２．相談趣旨
３．総合機構側指導・助言
４．その他（今後の予定等）
　（上記の事項について要点を述べる）

以上

This form will be used to develop a draft copy of the minutes from the consultation.

With this form, the company is required to summarize the consultation and include the following details:

- Date and time of consultation
- Place – PMDA Room Number, etc.
- Designated orphan drug name (product name)
- Designation number and date
- Possible efficacy/indications
- Participants – PMDA representative(s) name, personnel from the company, etc.
- Summary of discussion
    - Background information
    - Question/ topics the company covered in the consultation
    - Advice and comments from the PMDA regarding the questions above
    - Additional comments – future plans, etc.

### 5.4.9 Financial Aid

#### *5.4.9.1 Application Process*

While drug companies may be granted orphan drug designation at any time during the year, companies generally receive their financial aid from the MHLW in May. (Since the Japanese fiscal year begins in April, the MHLW allocates financial aid funds in April and makes them available in May.) However, if the MHLW has additional or leftover funds available later in the fiscal year (December, January, etc.) the MHLW may go ahead and distribute them at that time. The PMDA provides drug companies with a seminar about financial support in June.

When applying for financial aid, a company is required to submit a very detailed protocol of its clinical trial plan and the expected costs broken down into yearly quarters. If NIBIO approves the application, the financial aid will be granted between August and September of the same year. Normally, the Japanese government will assess the grant amount at half the company's expenses (as defined below). It should be noted that the government expects payroll to be no more than 30% of total expenses.

In most cases, the MHLW can finance three years of research. However, if any orphan drug projects are cancelled or put on hold during the middle of a fiscal year, the MHLW might be able to use those excess funds to provide a second financial aid grant to companies demonstrating good progress around December or January.

#### *5.4.9.2 What expenses does the financial aid cover?*

NIBIO provides detailed guidelines on the financial aid application process for orphan drug applicants. Visit http://www.nibio.go.jp/shinko/orphan/kisyo_tebiki20.pdf for more information (Japanese only).

The financial aid covers the expenses incurred from the orphan drug development process, such as the following:

- Clinical trial costs
- Travel expenses
- Equipment costs
- Printing fees
- Communication fees
- Leasing or user fees
- Refreshments / boxed lunches at critical meetings
- Payroll
- Consumables (including investigational drug, test materials, animals, animal feed, etc.)
- Sub-contracting fees

**Table 6: Approximate Schedule for Financial Aid Grant Process**

| Description | Approximate Date Range |
|---|---|
| Briefing Session | Late April |
| Submission of application form for aid | Mid-May |
| Hearing | May to June |
| Determination notice about the grant (for first application in the fiscal year) | July |
| Acceptance of an approximate bill and payment of the first credit | Late July |
| On-site inspection and progress confirmation | October to November |
| Application for changes in the research plan (acceptance for new applications in middle of the fiscal year) | December |
| Hearing and on-site inspection (for new applications in the middle of the fiscal year) | December to January |
| Determination notice about the grant (for new applications in the middle of the fiscal year) | January |
| Acceptance of an approximate bill and payment of the second credit | February |
| Submission of outcome report | By March 31st |
| Determination and refund notice | Late April |

#### *5.4.9.3 How is the financial aid overseen?*

Financial aid for orphan drug developers is managed by NIBIO. Pharmaceutical companies should provide a project/research update to NIBIO on a regular basis and notify NIBIO of any project delays or substantive changes to the development plan or situation. In the case of a delay (or project cancellation), NIBIO may ask the company to return the financial aid money or may charge the company late fees.

### 5.4.10 Reimbursement

Orphan drug designation can be grounds for an increase in the price reimbursed by Japan's national health insurance system (NHI). Since Japan's national health insurance is universal, this can significantly improve sales prospects.

Reimbursement levels for drugs and medical devices are recommended by the Central Social Insurance Medical Council (Chuikyo), and enacted based on that recommendation by the Minister of Health, Labor and Welfare. Chuikyo is a consultative council made up of representatives of the government (7), the medical profession (7), the public (6), and various other specializations (10). Prices for all drugs and devices are reviewed and adjusted every two years, while the procedure for an initial price for a newly marketed drug is separate. Chuikyo tends to reduce the costs of existing drugs in an attempt to

prevent the aging population from making healthcare spending unaffordable. Biennial price cuts generally average 4-7%. Innovator products usually see cuts of 1% or less, while generics face heavier price reductions.

Orphan drugs fall into the "marketability" reimbursement premium category. Products with orphan designation are eligible for a 10% premium in calculating a price. However, this only applies if the orphan indication is the *primary* indication for which the drug is approved.

In addition, there are other, higher premium categories which orphan drugs may often fall into. Most of these are for new drugs only. Items to be proved in order to fit into these premium categories include:

a. Has a clinically useful new mechanism of action
b. Has greater efficacy and safety than other drugs in the same category
c. Improves treatment of the indicated disease or trauma
d. Is indicated for children
e. There are no existing drugs with similar indications

The exact premium category depends on how many of these items are fulfilled. The highest possible premium, at 50-100%, is for "innovativeness," i.e., for drugs that meet conditions a, b, and c.

### 5.4.11 Other Important Steps

It is important to keep in mind that while Japan has orphan drug legislation, this legislation has room for interpretation. The MHLW and PMDA make orphan drug designation and approval decisions on a case-by-case basis. This is especially true when determining the number of Japanese clinical trials required for approval.

In order to develop a protocol of clinical trials to be conducted in Japan, a company should identify key doctors who will conduct the study, as well as a Contract Research Organization (CRO) that will lead the study. Since there is a shortage of Japanese regulatory specialists, the number of available CROs may be limited.

The drug company may also want to begin the search for appropriate distributor candidates that may be interested in marketing the product in Japan. Keep in mind that either the company or the distributor may file the new drug application dossier. If the drug company does not have its own office in Japan, it will also need to select a Marketing Authorization Holder, which will be responsible for quality and post-marketing safety of the product in Japan.

## 5.5 HEALTH AUTHORITY CONTACT INFORMATION

Ministry of Health, Labor and Welfare
Address: Central Government Building No. 5, 19th Floor, 1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo, Japan 100-8916
Phone: +81-3-5253-1111
Email: www-admin@mhlw.go.jp
Website: http://www.mhlw.go.jp/english/index.html

Pharmaceutical and Medical Devices Agency
Address: Shin-Kasumigaseki Bldg., 6th Floor, 3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo, Japan 100-0013
Phone: +81-3-3506-9456 (general); +81-3-3506-9004 (orphan drug dept.)
Fax: +81-3-3506-9572 (general); +81-3-3506-9418 (orphan drug dept.)
Email: orphan@pmda.go.jp
Website: http://www.pmda.go.jp/english/index.html

National Institute of Biomedical Innovation
Address: 7-6-8 Saitoasagi, Ibaraki-shi, Osaka-fu, Japan 567-0085
Phone: +81-72-641-9811 (general); +81-72-641-9804 (orphan drug dept.)
Fax: +81-72-641-9812 (general); +81-72-641-9831 (orphan drug dept.)
Email: kisho-ph@nibio.go.jp
Website: www.nibio.go.jp/shinko/orphan.html

## 5.6 ORPHAN DRUG ASSOCIATIONS

The Japan Society of Human Genetics
Address: 1-5-45 Yushima, Bunkyo-ku, Tokyo, Japan 113-8510
Japan 113-8622
Phone: +81-3-5803-5820
Fax: +81-3-5803-0244
Email: JSHG@soteria.cc
Website: http://jshg.jp/e/index_e.html

*The Japan Society of Human Genetics (JSHG) was established to promote the research of human genetics through the establishment of guidelines on genetic testing and counseling. The JSHG holds an annual meeting every fall, as well as periodic lectures for the public.*

Japanese Society for Inherited Metabolic Diseases
Address: 1-1-1 Honjo, Kumamoto-shi, Kumamoto-ken, Japan 860-8556
Phone: +81-96-373-5191
Fax: +81-96-366-3471
Email: JSIMD@kumamoto-u.ac.jp
Website: http://square.umin.ac.jp/JSIMD/

*The Japanese Society for Inherited Metabolic Diseases (JSIMD) was established in 1984 to promote the study of inherited metabolic disorders and related topics. The JSIMD arranges annual conferences, scientific seminars and publications.*

Administrator of Orphan Drug Designation Evaluation and Licensing Division
Pharmaceutical and Food Safety Bureau, MHLW
Address: 1-2-2 Kasumigaseki, Chiyoda-Ku, Tokyo, Japan 110-8916
Fax: +81-3-3597-9535

## 5.7 ORPHAN DRUGS APPROVED IN JAPAN

Note: As of February 21, 2014

| Date Approved | Generic Name | Trade Name | Approved Indication | Date Designated | Company |
|---|---|---|---|---|---|
| 1/19/1994 | Albendazole | Eskazole Tablets | Echinococcosis (Hydatid disease) | 11/15/1993 | GlaxoSmithKline K.K. |
| 4/1/1994 | Pentostatin | Coforin | Remission of subjective and objective symptoms caused by the following disease; Adult T cell leukemia-lymphoma; Hairy cell leukemia. | 11/15/1993 | The Chemo-Sero-Therapeutic Research Institute, Yamasa Shoyu Co., Ltd. |
| 7/1/1994 | Dantrolene sodium | Dantrium | Syndrome malin. | 11/15/1993 | Yamanouchi Pharmaceutical Co., Ltd. |
| 7/1/1994 | Tacrolimus | Prograf Capsules 0.5mg, 1mg; Prograf injection 5mg | Treatment of graft versus host disease (GVHD) after bone marrow transplantation. | 11/15/1993 | Fujisawa Pharmaceutical Co., Ltd. |
| 7/1/1994 | Trientine hydrochloride | Metalite 250 Capsules | Treatment of patients with Wilson's disease who are intolerant of D-penicillamine. | 11/15/1993 | Tsumura & Co. |
| 10/5/1994 | Mecasermin (genetical recombination) | Somazon 10mg for injection | Improvement of growth retardation in patients with following diseases: Growth Hormone Resistant Isolated Growth Hormone Deficiency type 1A and Laron-type Dwarfism. | 11/15/1993 | Fujisawa Pharmaceutical Co., Ltd. |
| 10/5/1994 | Mecasermin (genetical recombination) | Somazon 10mg for injection | Improvement of hyperglycemia, hyperinsulinemia, acanthosis nigricans and hirsuties in patients with following diseases: Insulin Receptor Deficiency Type A, Insulin Receptor Deficiency Type B, Congenital Generalized Lipodystrophy, Leprechaunism, Rabson-Mendenhall Syndrome. | 11/15/1993 | Fujisawa Pharmaceutical Co., Ltd. |
| 10/5/1994 | Corticorelin (human) | hCRH "Mitsubishi" injection | Hormonal function tests of hypothalamic-pituitary-adrenocortical axis. | 11/15/1993 | Mitsubishi Pharmaceutical Corp. |
| 10/5/1994 | Vancomycin hydrochloride | Vancomycin hydrochloride 0.5g for injection | Enterocolitis due to methicillin/cephem-resistant Staphylococcus aureus | 11/15/1993 | Shionogi & Co., Ltd. |

| Date Approved | Generic Name | Trade Name | Approved Indication | Date Designated | Company |
|---|---|---|---|---|---|
| 10/5/1994 | Indometacin sodium | Indacin IV | The following disease, for which conservative therapy (e.g., fluid restriction, administration of diuretics etc.) is ineffective; patent ductus arteriosus in premature infants. | 11/15/1993 | Banyu Pharmaceutical Co., Ltd. |
| 1/20/1995 | Lyophilized biological prep-aration containing the cells of Strep-tococcus pyogenes treated with benzyl-penicillin potassium | Picibanil | Lymphangioma. | 11/15/1993 | Chugai Pharmaceutical Co., Ltd. |
| 1/20/1995 | Tretinoin | Vesanoid capsules | Acute promyelocytic leukemia. | 11/15/1993 | Chugai Pharmaceutical Co., Ltd. |
| 9/29/1995 | Ciclosporin | Sandimmun | Aplastic anemia (severe), pure red cell aplasia. | 11/15/1993 | Novartis Pharmaceutical K.K. |
| 9/29/1995 | Anti-human thymocyte immuno-globuline, equine | Lymphoglobulin injection 100mg | Severe/moderate aplastic anemia. | 11/15/1993 | Aventis Pharmaceutical Ltd. |
| 9/29/1995 | Anti-human T-lymphocyte immunoglobulin, rabbit | Zetbulin injection | Severe or moderate Aplastic anemia. | 11/15/1993 | Nippon Zoki Pharmaceutical Co., Ltd. |
| 1/31/1996 | Ciclosporin | Sandimmun | Nephrotic syndrome (frequent-relapsing and steroid-resistant types). | 11/15/1993 | Novartis Pharma K.K. |
| 4/16/1996 | Mesalazine | Pentasa tablets 250 | Crohn’s disease. | 11/15/1993 | Nisshin Kyorin Pharmaceutical Co., Ltd. |
| 4/16/1996 | Mesalazine | Pentasa tablets 250 | Ulcerative colitis. | 11/15/1993 | Nisshin Kyorin Pharmaceutical Co., Ltd. |
| 4/16/1996 | Tacrolimus | Prograf Capsules 0.5mg, 1mg; Prograf injection 5mg | Suppression of organ rejection in allogenic kidney transplantation. | 11/15/1993 | Fujisawa Pharmaceutical Co., Ltd. |

| Date Approved | Generic Name | Trade Name | Approved Indication | Date Designated | Company |
|---|---|---|---|---|---|
| 7/10/1996 | Freeze-dried BCG | Immunobladder intravesical | Superficial bladder cancer, carcinoma in situ of urinary bladder. | 11/15/1993 | Japan BCG Laboratory |
| 7/10/1996 | Alglucerase | Ceredase | Improvement symptoms of Type I Gaucher disease (e.g., anemia, thrombocytopenia, hepatosplenomegaly, and bone symptoms). | 11/15/1993 | Genzyme Japan K.K. |
| 8/9/1996 | Rifampicin | Rifampicin Capsules | Hansen's disease. | 4/1/1996 | Hishiyama Pharmaceutical Co., Ltd. |
| 8/9/1996 | Rifampicin | Rimactane Capsules | Hansen's disease. | 4/1/1996 | Novartis Pharmaceutical K.K. |
| 8/9/1996 | Rifampicin | Rifadin | Hansen's disease. | 4/1/1996 | Daiichi Pharmaceutical Co., Ltd. |
| 8/9/1996 | Rifampicin | Rifampicin Capsules | Hansen's disease. | 4/1/1996 | Nippon Hexal Corp. |
| 8/9/1996 | Rifampicin | Aptecin | Hansen's disease. | 4/1/1996 | Kaken Pharmaceutical Co., Ltd. |
| 8/9/1996 | Ofloxacin | Tarivid | Hansen's disease. | 4/1/1996 | Daiichi Pharmaceutical Co., Ltd. |
| 10/9/1996 | Botulinum Toxin Type A | Botox injection 100 | Blepharospasm. | 11/15/1993 | Allergan K.K. |
| 11/12/1996 | Clofazimine | Lampren Capsules 50mg | Hansen's disease. | 4/1/1996 | Novartis Pharma K.K. |
| 3/28/1997 | Foscarnet sodium hydrate | Foscavir Infusion Solution | Cytomegalovirus retinitis in patients with AIDS. | 4/1/1995 | AstraZeneca K.K. |
| 3/28/1997 | Indinavir sulfate ethanolate | Crixivan Capsules | AIDS, symptomatic and asymptomatic HIV infection disease less than 500/mm3 lymphocytes before treatment. | 4/1/1996 | Banyu Pharmaceutical Co., Ltd. |
| 4/22/1997 | Somatropin (genetical recombination) | Norditropin S 5mg, 10mg, 1.33mg, 8mg | Short stature with achondroplasia where epiphyseal fusion has not taken place | 7/1/1994 | Novo Nordisk Pharmaceutical Ltd. |

| Date Approved | Generic Name | Trade Name | Approved Indication | Date Designated | Company |
|---|---|---|---|---|---|
| 7/2/1997 | Somatropin (genetical recombination) | Genotropin 1.3mg, 5.3mg; Genotropin KabiQuick 0.7mg, 1.0mg, 1.3mg | Short stature due to chronic renal insufficiency without closed epiphyses. | 7/1/1994 | Pfizer Japan Inc. |
| 7/25/1997 | Stavudine (Sanilvudine) | Zerit Capsules | Acquired immunological deficiency syndrome (AIDS); symptomatic or asymptomatic HIV infection with CD4 lymphocyte count of 500/mm3 or less before treatment; in proviso, the treatment solely with sanilvudine shouldn't be selected as the primary choice. | 4/1/1995 | Bristol Pharmaceuticals K.K. |
| 7/25/1997 | Ganciclovir | Denosine Capsules 250 | Alternative to the intravenous formulation for maintenance treatment of CMV retinitis in patients with AIDS, in whom retinitis is stable; prevention of CMV retinitis in individuals with advanced HIV infection that CD4 Count 100/mm3. | 4/1/1996 | Tanabe Seiyaku Co., Ltd. |
| 9/5/1997 | Saquinavir mesylate | Invirase capsules | AIDS symptomatic and asymptomatic HIV infections of CD4 lymphocyte count less than 500cells/mm3. | 9/25/1996 | Chugai Pharmaceutical Co., Ltd. |
| 11/20/1997 | Ritonavir | Norvir Soft Capsule 100mg | For use in combination with nucleoside analog reverse transcriptase inhibitors for the treatment of AIDS, symptomatic and asymptomatic HIV infection with pre-treatment CD4 Lymphocyte count of 500/mm3 and under | 4/1/1996 | Abbott Japan Co., Ltd. |
| 3/6/1998 | Imiglucerase (genetical recombination) | Cerezyme | Improvement symptoms of Gaucher disease (e.g., anemia, thrombocytopenia, hepatosplenomegaly, and bone symptoms ). | 4/1/1996 | Genzyme Japan K.K. |
| 3/6/1998 | Nelfinavir mesilate | Viracept | HIV infection. | 12/20/1996 | Japan Tobacco, Inc. |
| 6/30/1998 | Interferon gamma1a (genetical recombination) | Imunomax-γ injection vial | Reducing the frequency and severity of serious infections associated with chronic granulomatous disease. | 11/15/1993 | Shionogi & Co., Ltd. |
| 9/25/1998 | Ritonavir | Norvir Liquid | For use in combination with nucleoside analog reverse transcriptase inhibitors for the treatment of AIDS, symptomatic and asymptomatic HIV infection with pre-treatment CD4 Lymphocyte count of 500/mm3 and under. | 4/1/1996 | Abbott Japan Co., Ltd. |

| Date Approved | Generic Name | Trade Name | Approved Indication | Date Designated | Company |
|---|---|---|---|---|---|
| 9/30/1998 | Sotalol | Sotacor Tablets | Life-threatening recurrent arrhythmia which is refractory to or unable to use other anti-arrhythmic drugs; Ventricular Tachycardia (VT) and Ventricular Fibrillation (VF). | 11/15/1993 | Bristol Pharmaceuticals K.K. |
| 9/30/1998 | Clarithromycin | Clarith tab .200; Clarith tab.50 for pediatric; Clarith dry syrup for pediatric; Klaricid tab .200 | Disseminated mycobacterium infection in AIDS patients. | 7/1/1994 | Taisho Pharmaceutical Co., Ltd., Abbott Japan Co., Ltd. |
| 11/27/1998 | Nevirapine | Viramune | HIV-1 infection. | 12/20/1996 | Nippon Boehringer Ingelheim Co., Ltd. |
| 12/25/1998 | Riluzole | Rilutek 50mg Tablets | Treatment of ALS; Suppression of ALS progression. | 11/15/1993 | Aventis Pharma Ltd. |
| 1/25/1999 | Epoprostenol sodium | Flolan for injection | Primary pulmonary hypertension | 7/1/1994 | GlaxoSmithKline K.K. |
| 3/12/1999 | Interferon beta | IFNβ Mochida | Inhibition of the progression of clinical symptoms in patients with subacute sclerosing panencephalitis in combination with inosine pranobex. | 7/1/1994 | Mochida Pharmaceutical Co., Ltd. |
| 3/12/1999 | Interferon Alfa | Sumiferon | Prevention of neurological worsening in subacute sclerosing panencephalitis (SSPE) in combination with inosine pranobex. | 7/1/1994 | Sumitomo Pharmaceutical Co., Ltd. |
| 3/12/1999 | Somatropin (genetical recombination) | Serostim 5mg | To increase and maintain lean body mass in patients with weight loss associated with HIV infection or AIDS that have a CD4 lymphocyte count of 200/mm3 or less. | 4/1/1995 | Serono Japan Co., Ltd. |
| 5/25/1999 | Phenylalanine reduced milk | Peptide Lophe | Phenylketonuria. | 7/1/1994 | Snow Brand Milk Products Co., Ltd. |
| 6/11/1999 | Clotrimazole | Empecid Troche | Oral candidiasis in HIV infectees (slight to moderate illness) | 3/27/1997 | Bayer Yakuhin Ltd. |
| 6/16/1999 | Freeze-dried poly-ethylene glycol treated human normal immuno-globulin | Kenketu glovenin-I-Nichiyaku | Improvement of muscle weakness caused by chronic inflammatory demyelinating polyneuropathy (CIDP) including multifocal motor neuropathy (MMN). | 7/1/1994 | Nihon Pharmaceutical Co., Ltd. |

| Date Approved | Generic Name | Trade Name | Approved Indication | Date Designated | Company |
|---|---|---|---|---|---|
| 6/16/1999 | Ursodeoxycholic acid | Ursosan tablets 50mg; Urso 100 | Improvement of liver function in primary biliary cirrhosis | 7/1/1994 | Mitsubishi Pharmaceutical Corp. |
| 9/10/1999 | (3S)-tetrahydro-3-fulyl N-(1S,2R)-3-(4-amino-N-isobutylbenzenesulfonamido)-1-benzyl-2-hydroxypropyl carbamate mono-methanesulfonate (Amprenavir) | Prozei Capsules | HIV-1 infection. | 4/1/1995 | Kissei Pharmaceutical Co., Ltd. |
| 9/10/1999 | Efavirenz | Stocrrin Capsules | HIV-1 infection. | 6/29/1999 | Banyu Pharmaceutical Co., Ltd. |
| 9/10/1999 | Abacavir | Ziagen Tablets | HIV infection. | 7/9/1999 | GlaxoSmithKline K.K. |
| 9/22/1999 | Piracetam | Myocalm oral administration liquid | To be taken in combination with other Anti-epilepsy drugs as therapy for cortical myoclonus. | 11/15/1993 | Taiho Pharmaceutical Co., Ltd., UCB Japan Co., Ltd. |
| 9/22/1999 | Mixture of L-arginine and L-arginine HCl (granule); L-arginine HCl (injectable) | Arge U Granule; Arge U Injection | Reduces the blood ammonia levels abruptly in congenital urea cycle disorders and congenital abnormalities in amino acid transfer cases where the granule cannot control its sudden rise caused by exhaustion. | 11/15/1993 | Ajinomoto Pharmaceutical Co., Ltd. |
| 9/22/1999 | Mycophenolate mofetil | CellCept capsules 250 | Treatment of intractable rejection after renal transplantation (when existing drug is ineffective and causes adverse reactions, and rejection was diagnosed as intractable); suppression of rejection after renal transplantation. | 7/1/1994 | Chugai Pharmaceutical Co., Ltd. |
| 9/22/1999 | Beraprost sodium | Dorner (Procylin) | Primary pulmonary hypertension. | 7/1/1994 | Toray Industries, Inc., Kaken Pharmaceutical Co., Ltd. |

| Date Approved | Generic Name | Trade Name | Approved Indication | Date Designated | Company |
|---|---|---|---|---|---|
| 1/18/2000 | Interferon Alfa | Sumiferon | HTLV-I associated myelopathy (HAM). | 11/15/1993 | Sumitomo Pharmaceuticals Co., Ltd. |
| 1/18/2000 | Cytarabine | Cylocide N injection | Remedy for acute leukemia induction therapy for relapse and refractory cases consolidation therapy. | 4/1/1996 | Nippon Shinyaku Co., Ltd. |
| 1/18/2000 | Botulinum Toxin Type A | Botox injection 100 | Single-sided face spasm. | 11/15/1993 | Allergan K.K. |
| 2/25/2000 | Delavirdine mesilate | Rescriptor tablets 200mg | HIV-1 infection. | 12/9/1999 | Pfizer Japan Inc. |
| 3/10/2000 | Eptacog alfa (activated) (genetical recombination) | NovoSeven 1.2mg, 4.8mg for injection | It is indicated for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX. | 7/1/1994 | Novo Nordisk Pharmaceutical Ltd. |
| 4/6/2000 | Saquinavir | Fortovase capsules | HIV-1 infection. | 11/24/1999 | Chugai Pharmaceutical Co., Ltd. |
| 7/3/2000 | Taltirelin | Ceredist Tablets 5 | Improvement of ataxia in spinocerebrallar degeneration (SCD). | 11/15/1993 | Tanabe Seiyaku Co., Ltd. |
| 9/22/2000 | Interferon beta-1b (genetical recombination) | Betaferon SC injection | Prevention of relapse and inhibition of progression in multiple sclerosis. | 7/1/1994 | Nihon Schering K.K. |
| 9/22/2000 | Tacrolimus hydrate | Prograf Capsules 0.5mg; 1mg | Generalized myasthenia gravis patients, after undergoing thymectomy, who received steroid therapy with insufficient efficacy or difficulty of dosing due to adverse reactions. | 3/4/1999 | Fujisawa Pharmaceutical Co., Ltd. |
| 12/12/2000 | Freeze-dried sulfonated human immunoglobulin | Kenketu Venilon-I | Guillain-Barre syndrome (severe cases with disturbance of gait due to acute exacerbation). | 4/1/1996 | The Chemo-Sero-Therapeutic Research Institute, Teijin Pharma Ltd. |
| 12/12/2000 | Lopinavir | Kaletra Liquid/ Kaletra Soft Capsule | HIV infection. | 9/20/2000 | Abbott Japan Co., Ltd. |
| 3/7/2001 | Didanosine | Videx EC Capsules | HIV infection. | 11/27/2000 | Bristol Pharmaceuticals K.K. |

| Date Approved | Generic Name | Trade Name | Approved Indication | Date Designated | Company |
|---|---|---|---|---|---|
| 4/4/2001 | Melphalan | Alkeran for injection | Preconditioning of haematopoietic stem cell transplantation in Leukemia, Malignant lymphoma, Multiple myeloma and Pediatric solid tumors. | 11/15/1993 | GlaxoSmithKline K.K. |
| 4/4/2001 | Mefloquine hydrochloride | Mephaquin SS Tablets 275, DJ 275 | Malaria. | 7/1/1994 | SSP Co., Ltd., Dojin Iyaku-Kako Co., Ltd. |
| 4/4/2001 | Gemcitabine hydrochloride | Gemzar for injection | Pancreatic carcinoma. | 4/1/1996 | Eli Lilly Japan K.K. |
| 4/4/2001 | Trastuzumab (genetical recombination) | Herceptin injection 150 | HER2 overexpression metastatic breast cancer. | 8/25/1999 | Chugai Pharmaceutical Co., Ltd. |
| 6/20/2001 | Botulinum Toxin Type A | Botox injection 100 | Spasmodic torticollis. | 11/15/1993 | Allergan K.K. |
| 11/21/2001 | Benzamide mono-methanesulfone | Glivec Capsules 100 mg | Chronic Myeloid Leukemia. | 12/20/2000 | Novartis Pharmaceutical K.K. |
| 12/13/2001 | Azithromycin hydrate | Zithromac tablets 600mg | Prevention and treatment of disseminated Mycobacterium avium complex (MAC) disease in persons with advanced HIV. | 12/20/2000 | Pfizer Japan Inc. |
| 1/17/2002 | Cladribine | Leustatin injection 8mg | Hairy cell leukemia. | 4/1/1995 | Janssen Pharmaceutical K.K. |
| 1/17/2002 | Infliximab | Remicade for IV infusion 100 | Treatment of patients with Crohn's disease with the following conditions (limited to those having an inadequate response to conventional therapy): patients with moderatery to severely active Crohn's disease; patients with fistulizing Crohn's disease. | 4/1/1996 | Tanabe Seiyaku Co., Ltd. |
| 1/17/2002 | Basiliximab | Simulect Injection 20mg | Inhibition of acute rejection after renal transplantation. | 8/25/1999 | Novartis Pharmaceutical K.K. |
| 1/17/2002 | Somatropin (genetical recombination) | Genotropin 1.3mg, 5.3mg; Genotropin KabiQuick 0.7mg, 1.0mg, 1.3mg | Short stature due to Prader-Willi Syndrome without closed epiphyses. | 6/16/2000 | Pfizer Japan Inc. |
| 1/17/2002 | Imidapril hydrochloride | Tanatril Tablets 2.5mg; Tanatril Tablets 5 mg | Type I Diabetic Nephropathy. | 12/20/2000 | Tanabe Seiyaku Co., Ltd. |

| Date Approved | Generic Name | Trade Name | Approved Indication | Date Designated | Company |
|---|---|---|---|---|---|
| 1/17/2002 | Chimeric anti-human TNF alfa monoclonal antibody | Remicade for IV infusion 100 mg | Treatment of Crohn's disease in patients with any of the following conditions, limited to cases where existing treatments are not sufficiently effective:<br>· Moderate to severe active stage<br>· External fistula | 4/1/1996 | Mitsubishi Tanabe Pharma Corporation |
| 7/5/2002 | Tiopronin | Thiola tablets 100 | Cystinuria. | 7/1/1994 | Santen Pharmaceutical Co., Ltd. |
| 10/8/2002 | Ivermectin | Stromectol Tablets 3mg | Intestinal Strongyloidiasis. | 11/27/1998 | Banyu Pharmaceutical Co., Ltd. |
| 7/17/2003 | Imatinib mesilate | Glivec Capsules 100mg | KIT (CD117) positive Gastrointestinal Stromal Tumor. | 10/2/2002 | Ciba-Geigy Japan Ltd. |
| 9/19/2003 | Rituximab | Rituxan | CD20 positive B-cell non-Hodgikin's Lymphoma. | 11/27/1998 | Zenyaku Kogyo Co., Ltd. |
| 10/9/2003 | Mesna | Uromitexan injection 100mg, Uromitexan injection 400mg | Prevention of urinary disorders (hemorrhagic cystitis, dysuria, etc.) associated with cyclophosphamide; a pretreatment regimen for hematopoietic stem cell transplantation. | 4/1/1995 | Shionogi & Co., Ltd. |
| 10/9/2003 | Cyclophosphamide | Endoxan injection 100mg;<br>Endoxan injection 500mg | Pretreatment for hematopoietic stem cell transplantation in the treatment of the following: Acute leukemia, Chronic myeloid leukemia, Myelodysplastic syndrome, Severe aplastic anemia, Lymphoma, Genetic disorders. | 4/1/1995 | Shionogi & Co., Ltd. |
| 10/16/2003 | Verteporfin (INN) | Visudyen | Age-related macular degeneration with subfoveal choroidal neovascularization. | 1/24/2002 | Novartis Pharmaceutical K.K. |
| 12/18/2003 | Atazanavir sulfate | Reyataz Capsules 150mg; Reyataz Capsules 200mg | HIV-1 infection. | 8/1/2003 | Bristol Pharmaceuticals Y.K. |
| 1/29/2004 | α-Galactosidase Agalsidase Beta (genetical recombination) | Fabrazyme 5mg, 35mg | Fabry disease. | 8/25/1999 | Genzyme Japan K.K. |

| Date Approved | Generic Name | Trade Name | Approved Indication | Date Designated | Company |
|---|---|---|---|---|---|
| 3/25/2004 | Tenofovir Disoproxil Fumarate | Viread tablets 300mg | HIV-1 infection. | 12/12/2003 | Japan Tobacco Inc. |
| 6/22/2004 | Epoprostenol sodium | Flolan injection 0.5mg or 1.5mg | Pulmonary arterial hypertension. | 6/17/2002 | GlaxoSmithKline K.K. |
| 10/22/2004 | Vancomycin hydrochloride | Vancomycin hydrochloride intravenous infusion | Sepsis, pneumonia, and purulent meningitis caused by Penicillin-resistant streptococcus pneumoniae (PRSP) sensitive to vancomycin hydrochloride. | 3/4/1999 | Eli Lilly Japan K.K. |
| 11/5/2004 | Valganciclovir | Valixa tablets 450mg | Treatment of CMB retinitis in AIDS patients. | 7/7/2004 | Tanabe Seiyaku Co., Ltd. |
| 12/24/2004 | Fosamprenavir Calcium Hydrate | Lexiva | HIV infection. | 10/13/2004 | GlaxoSmithKline K.K. |
| 3/23/2005 | Emtricitabine | Emtriva Capsules 200mg | HIV infection. | 10/13/2004 | Japan Tobacco Inc. |
| 4/11/2005 | Bosentan | Tracleer tablets 62.5mg | Pulmonary arterial hypertension (only WHO Group III or IV) | 1/31/2003 | Actelion Pharmaceuticals Japan Ltd. |
| 4/11/2005 | Baclofen (intrathecal) | Gabalon Intrathecal 0.005%, 0.05%, and 0.2% | Severe spasticity due to brain and spinal cord disease | 4/23/2001 | Daiichi Pharmaceutical Co., Ltd. |
| 4/11/2005 | Humanised anti-human interleukin-6 (IL-6) receptor monoclonal antibody (genetic recombination) | Actemra intravenous infusion 200mg | Castleman's disease. | 12/20/2000 | Chugai Pharmaceutical Co., Ltd. |
| 4/11/2005 | Tamibarotene | Amnolake tablet 2mg | Acute promyelocytic leukemia (APL). | 11/27/1998 | Toko Pharmaceutical IND. Co., Ltd. |
| 7/25/2005 | Humanized anti-CD33 monoclonal antibody (hp67.6 antibody)-calicheamicin conjugate | Mylotarg injection 5mg | Relapsed or refractory acute myelogenous leukemia. | 1/21/1999 | Wyeth K.K. |

| Date Approved | Generic Name | Trade Name | Approved Indication | Date Designated | Company |
|---|---|---|---|---|---|
| 1/23/2006 | Follitropin alfa (genetic recombination) | Gonal-F inection 75mg and 150mg | Male hypogonadotropic hypogonadism. | 9/20/2000 | Serono Japan Co., Ltd. |
| 7/26/2006 | Mozavaptane hydrochloride / OPC-31260 | Physuline tablets 30mg | Improvement of hyponatremia in patients with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). | 8/24/2001 | Otsuka Pharmaceutical Co., Ltd. |
| 7/26/2006 | Busulfan | Busulfex intravenous drip 60mg | Conditioning treatment prior to allogeneic hematopoietic stem cell transplantation. | 9/26/2003 | Kirin Brewery Co., Ltd. |
| 7/26/2006 | Interferon beta-1a | Avonex intramuscular injection 30mg syringe | Multiple sclerosis. | 3/4/1999 | Genzyme Japan K.K. |
| 10/20/2006 | Bortezomib | Velcade injection 3mg | Relapsed or refractory multiple myeloma. | 12/12/2003 | Janssen Pharmaceutical K.K. |
| 10/20/2006 | α-L-iduronidase | Aldurazyme intravenous drip 2.9mg | Reduction of symptoms in patients with mucopolysaccharidosis I. | 8/25/1999 | Genzyme Japan K.K. |
| 10/20/2006 | α-Galactosidase A | Replagal intravenous drip 3.5mg | Reduction of symptoms in patients with Fabry Disease. | 5/27/1999 | Dainippon Sumitomo Pharmaceuticals Co., Ltd. |
| 1/4/2007 | Doxorubicin HCl Liposome | Doxil injection 20mg | AIDS-related Kaposi's sarcoma | 5/8/2006 | Janssen Pharmaceutical K.K. |
| 1/26/2007 | Amiodarone hydrochloride | Ancaron injection 150mg | Recurrent and life-threatening ventricular fibrillation and hemodynamically unstable ventricular tachycardia. | 6/17/2003 | Sanofi Aventis K.K. |
| 1/26/2007 | Tacrolimus hydrate | Prograf capsule 0.5mg and 1mg | Lupus nephritis. | 12/2/2002 | Astellas Pharma K.K. |
| 1/26/2007 | Infliximab | Remicade IV 100mg | Bechet's disease with refractory uveoretinitis (patients having an inadequate response to conventional therapy). | 3/15/2002 | Tanabe Seiyaku Co. Ltd. |
| 1/26/2007 | Modafinil | Modiodal tablets 100mg | Narcolepsy. | 1/6/2000 | Alfresa Pharma Corp. |
| 1/26/2007 | Pegvisomant | Somavert injection 10mg, 15mg, and 20mg | Acromegaly | 5/28/2002 | Pfizer Japan Inc. |
| 4/18/2007 | Alglucosidase alfa | Myozyme drip injection 50mg | Glycogen storage disease type II. | 2/10/2006 | Genzyme Japan K.K. |

| Date Approved | Generic Name | Trade Name | Approved Indication | Date Designated | Company |
|---|---|---|---|---|---|
| 10/4/2007 | Idursulfase | Elaprase drip infusion 6mg | Mucopolysaccharidosis Type II. | 12/14/2006 | Genzyme Japan K.K. |
| 10/19/2007 | Nelarabine | Arranon G injection 250mg | Adult or childhood T-cell acute lymphoblastic leukemia or T-cell acute lymphoblastic lymphoma. | 6/9/2006 | GlaxoSmithKline K.K. |
| 10/19/2007 | Avian influenza vaccine (H5N1) | Avian Influenza Vaccine (H5N1) "Biken" | Influenza (H5N1). | 6/9/2006 | Research Foundation for Microbial Diseases of Osaka University |
| 10/19/2007 | Avian influenza vaccine (H5N1) | Avian Influenza Vaccine (H5N1) "Hokken" | Influenza (H5N1) | 6/9/2006 | Kitasato Institute |
| 11/22/2007 | Darunavir ethanolate | Prezista Tablets 300 mg | HIV infection | 1/25/2007 | Janssen Pharmaceutical K.K. |
| 1/25/2008 | Sildenafil citrate | Revatio tablets 20mg | Pulmonary arterial hypertension | 2/27/2007 | Pfizer KK |
| 1/25/2008 | NPC-02 | Nobelzin capsules 25mg and 50mg | Wilson's disease | 11/5/2004 | Nobelpharma Co., Ltd. |
| 1/25/2008 | Ibritumomab tiuxetan | 1.Zevalin yttrium (Y) injection<br>2. Zevalin indium (In) injection | 1. Relapsed or refractory CD20- positive disease in low-grade B-cell non-Hodgkin's lymphoma and mantle cell lymphoma (MCL)<br>2. Confirmation of the accumulation site of ibritumomab tiuxetan（recombinant） | 1/13/2005 | Bayer Holding Ltd. |
| 1/25/2008 | Tacrolimus hydrate | Talimus eyedrops 0.1% | Vernal keratoconjunctivitis | 7/7/2004<br>12/13/2005 | Astellas Pharmaceutical Inc.<br>Senju Pharmaceutical Co., Ltd. |
| 3/28/2008 | Galsulfase (Genetic recombination) | Naglazyme drip infusion 5mg | Mucopolysaccharidosis Type VI | 6/5/2007 | AnGes MG |
| 6/6/2008 | Basiliximab | Simulect I.V. Injection 10mg | Supression of acute organrejection after renal transplantation | | Novartis Pharma K.K. |

| Date Approved | Generic Name | Trade Name | Approved Indication | Date Designated | Company |
|---|---|---|---|---|---|
| 6/24/2008 | Raltegravir potassium | Isentress tablets 400mg | HIV infection | 11/26/2007 | MSD K.K. |
| 7/16/2008 | Nitric oxide | INOflo for Inhalation 800ppm | Hypoxic respiratory failure (HRF) with concurrent pulmonary hypertension in neonates | 10/2/2002 | INO Therapeutics LLC |
| 7/16/2008 | Pegaptanib sodium | Macugen Ivt Inj. Kit 0.3mg | Age-related macular degeneration with concurrent choroidal neovascularization | 7/7/2004 | Pfizer Japan Inc. |
| 7/16/2008 | Anti-human thymocyte immunoglobulin, Rabbit | Thymoglobuline IV Infusion 25mg | Moderate to very severe aplastic anemia<br>Acute graft-versus-host disease (GVHD) after hematopoietic stem cell transplantation | 11/15/1993<br>7/1/1994 | Sanofi K.K. |
| 7/16/2008 | Sapropterin hydrochloride | Biopten granule 2.5% | Reduction of serum phenylalanine (Phe) levels in hyperphenylalaninemia (HPA) due to tetrahydrobiopterin (BH4)-responsive phenylalanine hydroxylase deficiency (BH4-responsive HPA) | 9/13/2007 | Daiichi Sankyo Company, Limited |
| 7/16/2008 | Risedronate sodium hydrate | Actonel tablet 17.5 mg<br>Benet tablet 17.5 mg | Paget's disease of bone | 6/9/2006 | Ajinomoto Co. Inc.<br>Takeda Pharmaceutical Co., Ltd. |
| 7/16/2008 | Argatroban | Novastan HI injection 10 mg/2 mL<br>Slonnon HI injection 10 mg/2 mL | Prevention of coagulation of blood during extracorporeal circulation in patients with heparin-induced thrombocytopenia (HIT) type II (hemodialysis), prevention of coagulation of blood in percutaneous coronary intervention (PCI) in patients with HIT type II (including patients at risk of HIT type II) and prophylaxis of thrombosis in patients with HIT type II | 3/22/2004 | Mitsubishi Tanabe Pharma Corporation<br>Daiichi-Sankyo Company, Limited |
| 10/16/2008 | Phenobarbital sodium IV | Noberbar 250mg for Injection | Neonatal seizures and status epilepticus | 3/24/2005 | Nobelpharma Co., Ltd. |
| 10/16/2008 | Pirfenidone (5-methyl-1-phenyl-2-(1H)-pyridone) | Pirespa tablets 200mg | Idiopathic pulmonary fibrosis | 9/4/1998 | Shionogi & Co., Ltd. |

| Date Approved | Generic Name | Trade Name | Approved Indication | Date Designated | Company |
|---|---|---|---|---|---|
| 10/16/2008 | Thalidomide | Thaled capsule 100 | Relapsed or refractory multiple myeloma | 2/8/2005 | Fujimoto Pharmaceutical Corporation |
| 10/16/2008 | Human thyrotropin alfa (recombinant | Thyrogen IM Injection 400mg | Support of diagnostics with radioactive iodine scintigraphy and serum thyroglobulin (Tg) test or with the Tg test alone in patients treated with total or semi-total thyroidectomy due to differentiated thyroid cancer. | 4/1/1996 | Genzyme Japan K.K |
| 12/15/2008 | Maraviroc | Celsentri tablets 150mg | CCR5-tropic HIV-1 infection | 8/4/2008 | ViiV Healthcare K.K. |
| 12/25/2008 | Etravirine | Intelence tablets 100mg | HIV-1 infection | 8/4/2008 | Janssen Pharmaceutical K.K. |
| 1/21/2009 | Ranibizumab | Lucentis Solution for Intravitreal Injection 2.3mg/0.23mL | Age-related macular degeneration with concurrent choroidal neovascularization | 3/10/2006 | Novartis Pharma K.K. |
| 1/21/2009 | Nilotinib hydrochloride hydrate | Tasigna capsules 150 mg and 200 mg | Imatinib-resistant, chronic phase and accelerated phase chronic myelogenous leukemia | 3/23/2007 | Novartis Pharma K.K. |
| 1/21/2009 | Dasatinib hydrate | Sprycel tablets 20mg and 50mg | Imatinib-resistant chronic myelogenous leukemia and recurrent or refractory Philadelphia chromosome-positive acute lymphoblastic leukemia | 3/23/2007 | Bristol-Myers K.K. |
| 10/16/2009 | Darunavir ethanolate | Prezistanaive Tablets 400 mg | Treatment of HIV infection | 1/25/2007 | Janssen Pharmaceutical K.K. |
| 10/16/2009 | Blood coagulation factor IX (recombinant) | BeneFIX IV injection 500 IU<br>BeneFIX IV injection 1000 IU<br>BeneFIX IV injection 2000 IU | Reduction of bleeding tendency in patients with hemophilia B (congenital blood coagulation factor IX deficiency) | 4/1/1996 | Pfizer Japan Inc. |

| Date Approved | Generic Name | Trade Name | Approved Indication | Date Designated | Company |
|---|---|---|---|---|---|
| 10/16/2009 | Vancomycin hydrochloride | Vancomycin Ophthalmic Ointment 1% | Treatment of conjunctivitis, blepharitis, meibomianitis, and dacryocystitis caused by vancomycin-sensitive methicillin-resistant Staphylococcus aureus (MRSA) and methicillin-resistant Staphylococcus epidermidis | 4/23/2001 | TOA Pharmaceutical Co. Ltd. |
| 10/16/2009 | Tacrolimus hydrate | Prograf capsule 0.5 mg<br>Prograf capsule 1 mg<br>Prograf granule 0.2 mg<br>Prograf granule 1 mg | Myasthenia gravis | 6/6/2008 | Astellas Pharma Inc |
| 1/20/2010 | Dried sulfonated human immunoglobulin | Kenketsu Venilon-I for IV injection 500 mg<br>Kenketsu Venilon-I for IV injection 1000 mg<br>Kenketsu Venilon-I for IV injection 2500 mg<br>Kenketsu Venilon-I for IV injection 5000 mg | Improvement of neuropathy in Churg-Strauss syndrome and allergic granulomatous angiitis (limited to cases for which steroid treatment is not sufficiently effective) | 12/11/2008 | Kaketsuken |
| 4/16/2010 | Eculizumab (recombinant) | Soliris for Intravenous Infusion 300 mg | Treatment to reduce hemolysis in patients with paroxysmalnocturnal hemoglobinuria | 12/22/2008 | Alexion Pharma K.K |
| 4/16/2010 | Infliximab (recombinant) | Remicade for IV infusion 100 mg | Ankylosing spondylitis for which existing treatments are not sufficiently effective | 6/6/2008 | Mitsubishi Tanabe Pharma Corporation |
| 6/25/2010 | Lenalidomide hydrate (CC-5013) | Revlimid Capsules 5mg | Treatment of relapsed or refractory multiplemyeloma | 2/18/2008 | Celgene K.K. |
| 7/23/2010 | Ambrisentan | Volibris Tablets 2.5 mg | Treatment of pulmonary arterial hypertension. | 5/16/2007 | GlaxoSmithKline K.K |
| 8/20/2010 | CC-5013 lenalidomide | Revlimid capsule 5 mg | Myelodysplastic syndrome with deletion on the long arm of chromosome 5 | 2/18/2008 | Celgene K.K. |
| 10/27/2010 | Bendamustine hydrochloride | Treakisym for IV infusion 100 mg | Relapsed or refractory cases of low-grade B-cell non-Hodgkin's lymphoma and mantle cell lymphoma (MCL) | 10/28/2009 | SymBio Pharmaceuticals Limited |

| Date Approved | Generic Name | Trade Name | Approved Indication | Date Designated | Company |
|---|---|---|---|---|---|
| 10/27/2010 | SB-497115-GR | Revolade tablet 12.5mg<br>Revolade tablet 25mg | Chronic idiopathic thrombocytopenic purpura | 3/23/2007 | GlaxoSmithKline K.K. |
| 10/27/2010 | Precipitated H5N1 influenza vaccine | H5N1 precipitated influenza vaccine "Kaketsuken" | Prophylaxis of H5N1 influenza | 6/9/2006 | Kaketsuken |
| 10/27/2010 | Polyethylene glycol-treated human immunoglobulin | Venoglobulin IH 5% IV injection 0.5 g/10 mL<br>Venoglobulin IH 5% IV injection 1 g/20 mL<br>Venoglobulin IH 5% IV injection 2.5 g/50 mL<br>Venoglobulin IH 5% IV injection 5 g/100 mL | Improvement of muscle weakness in polymyositis and dermatomyositis (limited to cases in which steroids are inadequate) | 1/6/2000<br>12/2/2002 | Japan Blood Products Organization |
| 1/21/2011 | Azacitidine | Vidaza for injection 100 mg | Myelodysplastic syndrome | 11/17/2008 | Nippon Shinyaku Co., Ltd. |
| 1/21/2011 | AMG531 | Romiplate SC injection 250 μg for preparative purpose | Chronic Idiopathic thrombocytopenic purpura | 8/11/2006<br>2/2/2010 | Kyowa Hakko Kirin Co., Ltd. |
| 5/20/2011 | Argatroban | Novastan HI injection 10 mg/2 mL<br>Slonnon HI injection 10 mg/2 mL | Prevention of coagulation of blood during extracorporeal circulation in patients with heparin-induced thrombocytopenia (HIT) type II (hemodialysis), prevention of coagulation of blood in percutaneous coronary intervention (PCI) in patients with HIT type II (including patients at risk of HIT type II) and prophylaxis of thrombosis in patients with HIT type II | 3/22/2004 | Mitsubishi Tanabe Pharma Corporation<br>Daiichi-Sankyo Company, Limited |
| 7/1/2011 | Vorinostat | Zolinza capsule 100 mg | Cutaneous T-cell lymphoma | 6/16/2010 | MSD K.K. |
| 8/17/2011 | Chimeric anti-human TNF alfa monoclonal antibody | Remicade for IV infusion | Treatment of Crohn's disease in patients with any of the following conditions, limited to cases where existing treatments are not sufficiently effective:<br>· Moderate to severe active stage<br>· External fistula | 4/1/1996 | Mitsubishi Tanabe Pharma Corporation |
| 9/16/2011 | Bortezomib | Velcade for injection 3 mg | Multiple myeloma | 11/10/2010 | Janssen Pharmaceutical K.K. |

| Date Approved | Generic Name | Trade Name | Approved Indication | Date Designated | Company |
|---|---|---|---|---|---|
| 9/26/2011 | Canakinumab | Ilaris for s.c. injection 150 mg | Cryopyrin-associated periodic syndrome in patients ≥2 years of age: familial cold autoinflammatory syndrome, Muckle-Wells syndrome, neonatal onset multi-organ inflammatory disease | 8/11/2010 | Novartis Pharma K.K |
| 9/26/2011 | Polyethylene glycol-treated human immunoglobulin | Venoglobulin IH 5% IV injection 0.5 g/10 mL<br>Venoglobulin IH 5% IV injection 1 g/20 mL<br>Venoglobulin IH 5% IV injection 2.5 g/50 mL<br>Venoglobulin IH 5% IV injection 5 g/100 mL | Generalized myasthenia gravis when post-thymectomy treatment with steroidal or non-steroidal immunosuppressive agents is not sufficiently effective | 9/11/2009 | Japan Blood Products Organization |
| 9/26/2011 | FTY720 | Imusera capsule 0.5 mg<br>Gilenya capsule 0.5 mg | Prevention of recurrence of, and inhibition of progression of physical disability in multiple sclerosis | 9/13/2007 | Mitsubishi Tanabe Pharma Corporation<br>Novartis Pharma K.K. |
| 2/22/2012 | Imatinib mesylate | Glivec tablet 100mg | FIP1L1-PDGFR α-positive hypereosinophilic syndrome and chronic eosinophilic leukemia | 12/14/2011 | Novartis Pharma K.K. |
| 3/30/2012 | Dornase alfa (recombinant) | Pulmozyme inhalation liquid 2.5 mg | Improvement of lung function in cystic fibrosis | 6/10/2011 | Chugai Pharmaceutical Co., Ltd. |
| 3/30/2012 | Miglustat | Brazaves capsule 100 mg | Niemann-Pick disease type C | 3/9/2011 | Actelion Pharmaceuticals Japan Ltd. |
| 3/30/2012 | Apomorphine hydrochloride hydrate | Apokyn SC injection 30 mg | Improvement of “off” symptoms in Parkinson's disease (when frequent administration of levodopa-containing preparations or increasing the dose of other antiparkinsonian agents is not sufficiently effective) | 3/9/2011 | Kyowa Hakko Kirin Co., Ltd. |
| 3/30/2012 | Crizotinib | Xalkori capsule 200 mg<br>Xalkori capsule 250 mg | Unresectable progressive or recurrent *ALK* fusion gene-positive non-small cell lung cancer | 1/28/2011 | Pfizer Japan Inc. |
| 3/30/2012 | KW-0761 | Poteligeo for IV infusion 20 mg | Relapsed or refractory CCR4-positive adult T-cell leukemia/lymphoma | 8/11/2010 | Kyowa Hakko Kirin Co., Ltd. |

| Date Approved | Generic Name | Trade Name | Approved Indication | Date Designated | Company |
|---|---|---|---|---|---|
| 5/18/2012 | Rilpivirine hydrochloride | Edurant tablet 25 mg | HIV-1 infection | 11/16/2011 | Janssen Pharmaceutical K.K. |
| 5/25/2012 | Thalidomide | Thaled capsule 50 mg<br>Thaled capsule 100 mg | Erythema nodosum leprosum | 12/14/2011 | Fujimoto Pharmaceutical Corporation |
| 5/25/2012 | Human thyrotropin alfa (recombinant | Thyrogen IM Injection 400mg | Support of ablation of residual tyroid by radioactive iodine in patients treated with total or semi-total thyroidectomy due to differentiated non-metastatic thyroid cancer | 4/1/1996 | Genzyme Japan K.K |
| 8/10/2012 | Sunitinib malate | Sutent capsule 12.5 mg | Pancreatic neuroendocrine tumor | 6/10/2011 | Pfizer Japan Inc. |
| 9/28/2012 | Pazopanib hydrochloride | Votrient tablet 200 mg | Malignant soft tissue tumors | 11/16/2011 | GlaxoSmithKline K.K. |
| 9/28/2012 | Stiripentol | Diacomit dry syrup 250 mg<br>Diacomit dry syrup 500 mg<br>Diacomit capsule 250 mg | Used in combination with clobazam and sodium valproate for tonic-clonic seizures or clonic seizure syndrome, for which clobazam and sodium valproate are not sufficiently effective, in patients with Dravet syndrome. | 3/9/2011 | Meiji Seika Pharma Co., Ltd. |
| 9/28/2012 | Preparation for implanting carmustine in the brain | Gliadel intracerebral implant 7.7 mg | Malignant glioma | 6/5/2009 | Nobelpharma Co., Ltd. |
| 9/28/2012 | Sodium phenylbutyrate | Buphenyl tablet 500 mg<br>Buphenyl Granule 94% | Urea cycle disorders | 9/12/2008<br>7/11/2011 | Orphan Pacific, Inc. |
| 11/21/2012 | Bosentan | Tracleer tablets 62.5mg | Pulmonary arterial hypertension (only WHO Group II, III, and IV) | 1/31/2003 | Actelion Pharmaceuticals Japan Ltd. |
| 11/21/2012 | Everolimus | Afinitor tablet 2.5 mg<br>Afinitor tablet 5 mg | Renal angiomyolipoma associated with tuberous sclerosis (only for tablet preparations)<br>Subependymal giant cell astrocytoma associated with tuberous sclerosis | 12/14/2011 | Novartis Pharma K.K. |

| Date Approved | Generic Name | Trade Name | Approved Indication | Date Designated | Company |
|---|---|---|---|---|---|
| 12/25/2012 | Everolimus | Afinitor dispersible tablet 2 mg<br>Afinitor dispersible tablet 3 mg | Renal angiomyolipoma associated with tuberous sclerosis (only for tablet preparations)<br>Subependymal giant cell astrocytoma associated with tuberous sclerosis | 12/14/2011 | Novartis Pharma K.K. |
| 12/25/2012 | Z-521 | Phosribbon combination granule | Hypophosphatemia | 3/19/2012 | Zeria Pharmaceutical Co., Ltd. |
| 12/25/2012 | Tetrabenazine | Choreazine tablet 12.5 mg | Chorea associated with Huntington's disease | 9/8/2011 | Alfresa Pharma Corporation |
| 3/25/2013 | Rufinamide | Inovelon tablet 100 mg<br>Inovelon tablet 200 mg | Combination therapy with antiepileptic drugs (AEDs) for tonic and atonic seizures in Lennox-Gastaut syndrome for which other AEDs are not sufficiently effective | 6/10/2011 | Eisai Co., Ltd. |
| 3/25/2013 | Ofatumumab (recombinant ) | Arzerra for IV infusion 100 mg<br>Arzerra for IV infusion 1000 mg | Relapsed or refractory CD20-positive chronic lymphocytic leukemia | 9/8/2011 | GlaxoSmithKline K.K. |
| 3/25/2013 | Hemin | Normosang for IV infusion 250 mg | Symptom relief during acute porphyria attacks | 9/8/2011 | OrphanPacific, Inc. |
| 3/25/2013 | Clofarabine | Evoltra for IV infusion 20 mg | Relapsed or refractory acute lymphocytic leukemia | 3/19/2012 | Sanofi K.K. |
| 3/25/2013 | Metreleptin | Metreleptin for SC injection "Shionogi" 11.25 mg | Lipoatrophy | 6/13/2012 | Shionogi & Co., Ltd. |
| 3/25/2013 | Cobicistat | Stribild combination Tablet *HC2911 | HIV-1 infection | 11/14/2012 | Japan Tobacco, Inc. |
| 3/25/2013 | Elvitegravir | Stribild combination tablet *HC2901 | HIV-1 infection | 11/14/2012 | Japan Tobacco, Inc. |
| 3/25/2013 | 5-Aminolevulinic acid hydrochloride | Alabel oral 1.5 g<br>Alaglio oral 1.5 g | Visualization of tumor tissue during surgical resection of malignant glioma | 9/14/2010<br>7/4/2012 | Nobelpharma Co., Ltd.<br>SBI Pharmaceuticals Co., Ltd. |
| 3/25/2013 | Precipitated H5N1 influenza vaccine | H5N1 precipitated influenza vaccine "SEIKEN”1 mL | Prophylaxis of H5N1 influenza | 6/9/2006 | Denka Seiken Co., Ltd. |

| Date Approved | Generic Name | Trade Name | Approved Indication | Date Designated | Company |
|---|---|---|---|---|---|
| 4/26/2013 | Cell culture-derived whole virion prototype vaccine | Cell culture influenza vaccine (prototype vaccine) "Baxter"<br>Cell culture influenza vaccine (prototype vaccine) "Takeda" 5mL | Prophylaxis for pandemic influenza | 9/13/2012 | Baxter Takeda Pharmaceutical Co., Ltd. |
| 6/14/2013 | Bevacizumab (recombinant) | Avastin for IV infusion 100 mg/4 mL<br>Avastin for IV infusion 400 mg/16 mL | Malignant glioma | 5/13/2013 | Chugai Pharmaceutical Co., Ltd. |
| 6/14/2013 | Tacrolimus hydrate | Prograf capsule 0.5 mg<br>Prograf capsule 1 mg | Interstitial pneumonia associated with polymyositis or dermatomyositis | 9/13/2012 | Astellas Pharma Inc. |
| 6/26/2013 | BLB-750 (H5N1 cell culture influenza vaccine) | H5N1 cell culture influenza vaccine "Baxter"<br>H5N1 cell culture influenza vaccine "Takeda" | Prophylaxis of H5N1 influenza | 6/16/2010<br>6/10/2011 | Baxter Takeda Pharmaceutical Co., Ltd. |
| 9/20/2013 | Talaporfin Sodium | Leserphyrin for injection 100 mg | Primary malignant brain tumor limited to cases treated with resection | 12/15/2008 | Meiji Seika Pharma Co., Ltd. |
| 9/30/2013 | Talaporfin sodium | Laserphyrin for injection 100 mg | Primary malignant brain tumor limited to cases treated with surgical resection | 8/12/2013 | Meiji Seika Pharma Co., Ltd. |
| 1/17/2014 | Betaine anhydrous | Cystadane powder | Homocystinuria | 3/19/2012 | ReqMed Company, Ltd. |
| 1/17/2014 | Riociguat | Adempas tablet 0.5mg<br>Adempas tablet 1.0mg<br>Adempas tablet 2.5mg | Unresectable or postoperative residual/recurrence Chronic thromboembolic pulmonary hypertension | 9/8/2011 | Bayer Holding Ltd. |
| 1/27/2014 | Brentuximab vedotin | Adetris for IV infusion 50mg | CD30-positive Hodgkin's lymphoma and anaplastic large cell lymphoma | 3/19/2012 | Takeda Pharmaceutical Co., Ltd. |
| 2/21/2014 | Cinacalcet hydrochloride | Regpara Tablet 25mg<br>Regpara Tablet 75mg | Hypercalcemia associated with parathyroid carcinoma or unresectable/postoperative recurrence primary hyperparathyroidism | 2/11/2012 | Kyowa Hakko Kirin Co., Ltd. |

## *5.8 Orphan Drugs Designated (not yet approved and designation not revoked) in Japan*

Note: Current to February 13, 2014

| Date Designated | Generic Name | Expected Indication | Company |
|---|---|---|---|
| 7/1/1994 | Indium111(111In) pentetreotide | Diagnosis of gastrointestinal hormone producing tumors by scintigraphy. | Marnicott Japan |
| 3/27/1997 | Fluconazole | Suppression of relapse of Cryptococcal Meningitis in patients with AIDS; Oropharyngeal candidiasis in patients with AIDS. | Pfizer Japan Inc. |
| 3/20/1998 | Doranidazole | Enhancement of the effect of intraoperative radiotherapy (IORT) for pancreatic cancer. | Pola Chemical Industries, Inc. |
| 4/3/2000 | Ganciclovir (Vitrasert Implant) | Cytomegalovirus retinitis in AIDS. | Bausch & Lomb Japan Co., Ltd. |
| 5/29/2003 | Intravitreal fluocinolone acetonide implant | Non-infectious uveitis affecting to posterior segment of the eye. | Bausch & Lomb Inc. |
| 10/13/2004 | FTY-720 | Renal transplantation. | Mitsubishi Tanabe Pharmaceutical Corp., Novartis Pharmaceutical K.K. |
| 6/20/2005 | Edaravone | Amyotrophic Lateral Sclerosis (ALS). | Mitsubishi Tanabe Pharmaceutical Corp. |
| 6/9/2006 | Leuprorelin acetate | Spinobulbar muscular atrophy. | Takeda Pharmaceutical Co. Ltd. |
| 8/11/2006 | Tolvaptan | Polycystic kidney disease. | Otsuka Pharmaceutical Co., Ltd. |
| 2/18/2008 | OPC-67683 | Pulmonary tuberculosis | Otsuka Pharmaceutical Co., Ltd. |
| 5/21/2008 | Natalizumab | Inhibiting progress of and preventing relapse of multiple sclerosis with sole administration | Biogen Idec Japan |
| 6/6/2008 | Forodesine hydrochloride | The following diseases when recurrent or intractable:<br>・Peripheral T-cell lymphoma<br>・Adult T-cell leukemia / lymphoma<br>・Cutaneous T-cell lymphoma<br>・T-cell acute lymphatic leukemia / T-cell lymphoblastic lymphoma | Mundi Pharma |
| 9/12/2008 | GSK1557484A (pandemic H5N1 influenza virus vaccine with adjuvant added prior to use) | Prophylaxis of H5N1 influenza | GlaxoSmithKline K.K. |

| Date Designated | Generic Name | Expected Indication | Company |
|---|---|---|---|
| 2/9/2009 | MC710 (freeze dried human blood coagulation factor X added to activated blood coagulation factor VII) | Inhibition of bleeding in patients with congenital hemophilia who have inhibitors to blood coagulation factor VIII or IX | Kaketsuken |
| 3/10/2009 | Glatiramer acetate | Reduction of recurrence frequency in relapsing-remitting multiple sclerosis (MS) | Teva Pharmaceutical K.K. |
| 5/12/2009 | Levodopa-carbidopa formulation for duodenal administration | 1. Parkinson's disease with severe mobility complications (Hoehn & Yahr severity stage IV or V, with wearing-off, no on/delayed on, or on-off phenomena, dyskinesia) when conventional oral therapy is not sufficiently effective<br>2. Parkinson's disease at Hoehn & Yahr severity stage I, II or III, but limited to cases where gastrostomy has already been performed due to dysphagia or for other reasons so that oral therapy is difficult | Solvay Pharmaceuticals, Inc. (AbbVie) |
| 6/16/2010 | Midismase (recombinant) | Idiopathic pulmonary fibrosis | LTT Bio-Pharma Co., Ltd. |
| 11/10/2010 | Bortezomib | Mantle cell lymphoma | Janssen Pharmaceutical K.K. |
| 11/10/2010 | Colistin sodium methanesulfonate | Indicated bacterial strains: Multidrug-resistant Pseudomonas aeruginosa (MDRP), multi-drug resistant Acinetobacter and other multidrug-resistant Gram-negative bacteria that are sensitive to this drug<br>Indications: Various infectious diseases | GlaxoSmithKline K.K. |
| 11/10/2010 | GSK2402968 | Duchenne muscular dystrophy | GlaxoSmithKline K.K. |
| 3/9/2011 | Genz-112638 | Type 1 Gaucher disease | Genzyme Japan K.K. |
| 6/10/2011 | Trabectedin | Malignant soft tissue tumors with chromosomal translocation | Taiho Pharmaceutical Co., Ltd. |
| 8/8/2011 | Caffeine citrate | Primary apnea in premature and low birth weight infants (apnea of prematurity) | Nobelpharma Co., Ltd. |
| 9/8/2011 | Ruxolitinib | Myelofibrosis | Novartis Pharma K.K. |
| 9/8/2011 | BIBF 1120 | Idiopathic pulmonary fibrosis | Nippon Boehringer Ingelheim Co., Ltd. |
| 11/16/2011 | Streptozocin | Pancreatic and gastrointestinal neuroendocrine tumors | Nobelpharma Co., Ltd. |
| 12/14/2011 | Tafamidis meglumine | Transthyretin amyloid polyneuropathy (familial amyloid polyneuropathy) | Pfizer Japan Inc. |
| 2/15/2012 | Pasireotide pamoate | Cushing's disease | Novartis Pharma K.K. |
| 3/19/2012 | Imatinib mesylate | Pulmonary arterial hypertension | Novartis Pharma K.K. |

| Date Designated | Generic Name | Expected Indication | Company |
|---|---|---|---|
| 3/19/2012 | Recombinant von Willebrand factor (Rvwf) | Reduction of bleeding tendency in patients with von Willebrand disease | Baxter |
| 3/19/2012 | Rurioctocog alfa (recombinant) | Reduction of bleeding tendency in patients with von Willebrand disease with decreased plasma concentration of blood coagulation factor VIII through plasma supplementation with blood coagulation factor VIII | Baxter |
| 5/11/2012 | Interferon gamma-1a (recombinant) | Mycosis fungoides (not during visceral dissemination stage) and Sézary syndrome | Shionogi & Co., Ltd. |
| 5/11/2012 | MPR-1020 | Nephropathic cystinosis | Mylan Seiyaku Ltd. |
| 5/11/2012 | Eprodisate disodium | AA amyloidosis | C. T. Development Swiss Corp. (A. T. Development Swiss Corp.) |
| 6/13/2012 | Bendamustine hydrochloride | Chronic lymphocytic leukemia | SymBio Pharmaceuticals Limited |
| 6/13/2012 | Type A influenza HA vaccine emulsion cell culture (H5N1 strain) | Prophylaxis of H5N1 influenza | Kaketsuken |
| 6/13/2012 | Type A influenza HA vaccine emulsion cell culture (prototype) | Prophylaxis for new strains of influenza | Kaketsuken |
| 6/13/2012 | Miglustat Hydrochloride | Fabry's disease | GlaxoSmithKline K.K. |
| 8/16/2012 | Ecallantide | Acute attacks of hereditary angioedema | CMIC Holdings Co., Ltd. |
| 8/16/2012 | Lenvatinib mesylate | Thyroid cancer | Eisai Co., Ltd. |
| 8/16/2012 | Alemtuzumab (recombinant) | Chronic lymphocytic leukemia | Sanofi-aventis K.K. |
| 8/16/2012 | SBC-102 | Lysosomal acid lipase deficiency | Synageva BioPharma Corp |
| 9/13/2012 | Rituximab (recombinant) | Refractory nephrotic syndrome | Zenyaku Kogyo Co., Ltd. |
| 9/13/2012 | Infliximab (recombinant) | Refractory Kawasaki disease | Mitsubishi Tanabe Pharma Corporation |
| 9/13/2012 | Infliximab (recombinant) | Intestinal, neuro-, and vasculo Behcet syndrome | Mitsubishi Tanabe Pharma Corporation |
| 9/13/2012 | Sirolimus | Lymphangioleiomyomatosis (LAM) | Nobelpharma Co., Ltd. |
| 9/13/2012 | Vemurafenib | $BRAF^{V600}$ mutation-positive malignant melanoma | Chugai Pharmaceutical Co., Ltd |
| 11/14/2012 | Dried polyethylene glycol-treated human | Stevens-Johnson syndrome and toxic epidermal necrolysis (for which systemic steroid treatment is not sufficiently effective) | Nihon Pharmaceutical Co., Ltd. |
| 11/14/2012 | SAR302503 | Myelofibrosis | Sanofi K.K. |
| 12/11/2012 | BMN110 | Mucopolysaccharidosis Type IV A | BioMarin Pharmaceutical Inc. |
| 12/11/2012 | Precipitated influenza vaccine cell culture (H5N1 strain) | Prophylaxis of H5N1 influenza | Kitasato Daiichi Sankyo Vaccine Co., Ltd. |

| Date Designated | Generic Name | Expected Indication | Company |
|---|---|---|---|
| 12/11/2012 | Precipitated influenza vaccine cell culture (prototype vaccine) | Prophylaxis for new strains of influenza | Kitasato Daiichi Sankyo Vaccine Co., Ltd. |
| 3/15/2013 | Mogamulizumab（recombinant） | Peripheral T-cell lymphoma, cutaneous T-cell lymphoma | Kyowa Hakko Kirin Co., Ltd. |
| 3/15/2013 | Bexarotene | Cutaneous T-cell lymphoma | Minophagen Pharmaceutical Co., Ltd |
| 3/15/2013 | Ipilimumab | Malignant melanoma | Bristol-Myers |
| 5/13/2013 | Aminolevulinic acid hydrochloride | Visualization of tumor tissue during surgical resection of non-muscle invasive bladder cancer | Nobelpharma Co., Ltd.<br>SBI Pharmaceuticals Co., Ltd. |
| 5/13/2013 | Rifaximin | Hepatic encephalopathy | ASKA Pharmaceutical. Co., Ltd. |
| 5/13/2013 | Ozanezumab | Amyotrophic lateral sclerosis (ALS) | GlaxoSmithKline K.K. |
| 6/17/2013 | Dried sulfonated human immunoglobulin | Optic neuritis (for which steroid treatment is not sufficiently effective) | Kaketsuken, Teijin Pharma Limited |
| 6/17/2013 | Denosumab (recombinant) | Giant cell tumor of bone | Daiichi Sankyo Company, Limited |
| 6/17/2013 | Ambrisentan | Chronic thromboembolic pulmonary hypertension | GlaxoSmithKline K.K. |
| 6/17/2013 | ONO-4538 | Malignant melanoma | Ono Pharmaceutical Co., Ltd. |
| 9/3/2013 | Lomitapide mesylate | Homozygous familial hypercholesterolemia (HoFH) | Aegerion Pharmaceuticals, Inc. |
| 9/3/2013 | Rituximab (recombinant) | Chronic idiopathic thrombocytopenic purpura | Zenyaku Kogyo Co., Ltd. |
| 9/3/2013 | BYM338 | Inclusion body myositis | Novartis Pharma K.K |
| 9/13/2013 | Mepolizumab | Churg-Strauss syndrome | GlaxoSmithKline K.K. |
| 9/13/2013 | Dolutegravir sodium | HIV infection | ViiV Healthcare K.K. |
| 9/13/2013 | Sorafenib tosylate | Thyroid cancer | Bayer Holding Ltd. |
| 9/13/2013 | Alectinib hydrochloride | Unselectable progressive or recurrent *ALK* fusion gene-positive non-small cell lung cancer | Chugai Pharmaceutical Co., Ltd. |
| 9/13/2013 | Trametinib | $BRAF^{V600}$ mutation-positive malignant melanoma | GlaxoSmithKline K.K. |
| 9/13/2013 | Dabrafenib | $BRAF^{V600}$ mutation-positive malignant melanoma | GlaxoSmithKline K.K. |
| 11/15/2013 | Propranolol hydrochloride | Infantile hemangiomas | Maruho Co., Ltd. |
| 12/4/2013 | Human C1 inhibitor | Prevention and treatment of angioedema episodes in patients with human C1 inhibitor (C1 INH) deficiency due to heredity or spontaneous mutations | ViroPharma Incorporated |
| 12/4/2013 | Vandetanib | Thyroid cancer | AstraZeneca K.K. |
| 12/4/2013 | MEK162 | *NRAS* or $BRAF^{V600}$ mutation-positive malignant melanoma | Novartis Pharma K.K. |
| 12/4/2013 | LGX818 | $BRAF^{V600}$ mutation-positive malignant melanoma | Novartis Pharma K.K. |
| 12/4/2013 | Bosutinib hydrate | Chronic myelogenous leukemia with resistance or intolerance to previous treatments | Pfizer Japan Inc. |

| Date Designated | Generic Name | Expected Indication | Company |
|---|---|---|---|
| 12/12/2013 | NPR-01 | External fistulas due to Crohn's disease (including anal fistulas) | Nihon Pharmaceutical Co., Ltd. |
| 12/12/2013 | JR-031 | Acute graft-versus-host disease | Japan Chemical Research Co., Ltd. |
| 12/12/2013 | Modafinil | Excessive daytime sleepiness associated with idiopathic hypersomnia | Alfresa Pharma Corporation |

# 6. TAIWAN

## 6.1 OVERVIEW

Taiwan's pharmaceutical market is valued at around $5.4 billion and the Taiwanese government is continuing to improve drug regulations and standards in order to attract more foreign enterprises and investment. About 70% of drugs sold in Taiwan are from global pharmaceutical companies, though only about 40% of all drugs are imported.

The health standards in Taiwan are among the best in Asia. The country also boasts a high life expectancy – about 77 years for men and 83 for women. By the end of 2013, Taiwan had about 35,000 Western hospitals and clinics, with about 70 hospital beds for every 10,000 citizens.

## 6.2 TAIWANESE HEALTH AUTHORITIES

Taiwan's Ministry of Health and Welfare (MOHW) is responsible for ensuring the availability and efficiency of medical treatment in Taiwan. The MOHW monitors the National Health Insurance program, hospital operations and coordinates among local health agencies.

The Taiwan Food and Drug Agency (TFDA) is in charge of establishing laws and policies on the management of pharmaceuticals in Taiwan, including the following responsibilities:

- Issue licenses for importing, exporting, supplying, manufacturing and selling pharmaceuticals
- Supervise the inspection of controlled drugs by local health authorities
- Manage the drug testing laboratory certification system in Taiwan
- Investigate and report on pharmaceutical abuse by providing early warnings and education on pharmaceuticals

In addition to the TFDA, the Center for Drug Evaluation (CDE) also assists with the review and evaluation of new drug applications in Taiwan. Established in 1998, the CDE is a non-governmental and non-profit organization. The CDE not only provides a source of professional application reviewers for the MOHW, but also helps with clinical trial consultations and the establishment of new pharmaceutical regulatory requirements in Taiwan. CDE consultation sessions are usually held via teleconferences or face-to-face meetings. Some of the regulations drafted by the CDE and implemented by the MOHW are as follows:

- Guideline on the Application and Operational Standards for Gene Therapy (September 2002)
- Guideline on Necessary Documents to Apply for Clinical Trials (June 2002)
- Good Clinical Trial Guidelines (August 2002)

The TFDA and the CDE have set up an Integrated Medicinal Products Review Office (iMPRO) to bring together all product review processes into a more efficient and evidence-based scientific review platform. This office evaluates all investigational new drug (IND) clinical trial applications, new drug applications (NDAs), generic drug applications (ANDAs), drug master file applications, and bridging study evaluations. A team of reviewers made up of TFDA and CDE personnel will review application documents and have meetings to discuss cases. In the case of safety concerns or a deficiency in the application, the case will be forwarded to the advisory committee for continued discussion. TFDA officials make final case decisions and notify the applicants of application results.

## 6.3 HEALTH INSURANCE SCHEME

The National Health Insurance Administration (NHIA) is responsible for health insurance in Taiwan. Established in 1995, the NHIA now provides affordable health coverage to about 99% of the country's citizens and has a public satisfaction rate of 80%. Prior to the establishment of the NHIA, three different insurance systems were in effect, offering nearly a dozen different insurance programs. These programs were only available to labor, government, and agricultural workers and in total, only about 60% of the country's total population was covered by health insurance.

Today, the NHIA, which is overseen by the MOHW, is a mandatory insurance system. All Taiwanese citizens are required to join the program; foreigners with Taiwan resident permits and their dependents are also eligible for enrollment. Premium contributions are shared between the insured, their employer and the Taiwanese government. The scheme covers the majority of medical expenses, with the exception of transportation, registration fees, blood and plastic surgery.

## 6.4 ORPHAN DRUGS IN TAIWAN

### 6.4.1 Orphan Drug Definition and Legislation

On February 9, 2000, Taiwan's Legislative Yuan implemented the *Rare Disease and Orphan Drug Act* to improve the diagnosis, treatment and prevention of rare diseases in Taiwan. In particular, the Act aims to provide patients with easier access to pharmaceuticals for the treatment of rare diseases by promoting the supply, manufacturing and R&D of these products. To carry out the Act, the MOHW established the *Committee for the Review and Examination of Rare Diseases and Orphan Drugs* (the Committee). The Committee is made up of citizens, medical specialists and government representatives, and is responsible for the following:

- Identifying rare diseases
- Reviewing and approving orphan drug applications
- Testing and marketing orphan drugs
- Examining orphan drug funding and R&D

The Act defines orphan drugs as pharmaceuticals whose *primary* indication(s) is/are for the prevention, diagnosis and treatment of rare diseases. Previously, pharmaceuticals with orphan drug designation from other countries could also be considered, but this was removed by an amendment in 2005. The MOHW considers a disease or condition to be a "rare disease" if the prevalence rate is less than 0.01% of the population (1 in 10,000), which is equivalent to about 2,300 cases.

Prior to the enactment of the *Rare Disease and Orphan Drug Act*, rare disease patients in Taiwan had limited information on their medical conditions. There was also a shortage of medical specialists to treat them. Orphan drugs were also less accessible and expensive. More importantly, these drugs were not reimbursed by health insurance. After the Act was implemented in 2000, Taiwan adopted a more comprehensive approach to rare diseases by developing genetics consultation, stepping up the prevention of rare diseases and increasing medical welfare. There has also been greater international cooperation and public awareness regarding the availability of orphan drug treatments.

In December 2004, there were about 4,200 people with rare disease, certified by the Taiwan government. By 2011, the number had increased to more than 6,000. The combined medical costs for people with rare disease totaled about $22 million (NT$640 million) per year. Out of this, drug fees accounted for about 66%.

The MOHW is constantly striving to encourage the registration of orphan drugs in Taiwan. Since implementation, the MOHW has carried out the following additional programs to promote awareness of and research in rare diseases:

- Set up a central reporting system for patients and medical practitioners to report incidence of rare conditions, which by 2006 had logged over 2,000 cases, and issued public citations to encourage reporting
- Requested the Taiwan Human Genetics Society to draft a plan to treat patients with metabolic disorders
- Established a program to subsidize some patients to go overseas for disease testing, with an average of 42 cases of year costing $1,000,000 NT ($33.838)
- Set aside funding to pay for rare disease-related medical expenses not covered by the National Health Insurance program
- Established a central counseling window for rare disease patients
- Established an orphan drug distribution center, initially stocking nine orphan drugs of critical importance
- Commissioned the Taiwan Foundation for Rare Disorders to produce a TV series about patients with rare diseases, "Born Fighters – Life Stories of Rare Diseases Patients"

In January 2005, an amended version of the *Rare Diseases and Orphan Drug Act* came into effect. Its main changes were:

- Removing products from consideration for orphan drug status simply because of their foreign orphan drug status

- Adding more support, similar to that for orphan drugs, for special nutrients that are medically necessary for rare disease patients
- Enabling rare disease patients to apply directly to the government for subsidies to go abroad for medical reasons.

In 2011, the Taiwanese government officially categorized 184 diseases as "rare diseases". Thus far, 74 orphan drugs and 40 special nutrients have been approved by the government for treatment of patients.

### 6.4.2 Orphan Drug Registration and Approval Process

Pharmaceuticals designated as orphan drugs are not required to undergo clinical trials for approval in Taiwan, as long as the drug has already been approved by the US FDA. If the drug has not received US FDA approval, local clinical trials will be required in Taiwan. The application must be submitted by a subsidiary of the manufacturer who has an office in Taiwan or a local Taiwanese agent (local distributor, local company office or independent third party). Application requirements are listed below in 6.4.3. The MOHW review process takes 6-10 months to complete.

In Taiwan, pharmaceuticals approved as orphan drugs are granted a 10-year marketing exclusivity period, wherein the MOHW will not accept registration applications for any similar drugs. However, under the following types of special circumstances, it may be possible for other similar drugs to be registered during this period:

- The new applicant has received permission from the license holder of the currently approved orphan drug
- The new applicant can prove that the safety and efficacy of their similar drug is superior to the orphan drug currently on the market
- The license owner of the currently marketed orphan drug cannot meet the demand of the drug
- The current market price of the orphan drug is considered unreasonable by the MOHW

Once the 10-year exclusivity period has expired, the approval license may be renewed in five year increments. During the extension periods, the product does not have marketing exclusivity: similar pharmaceuticals *can* be registered with the MOHW and marketed in Taiwan.

### 6.4.3 Taiwan's Orphan Drug Application Requirements

| | Required Documents and Information | Details |
|---|---|---|
| **1** | Application form | In Chinese (traditional characters) |
| **2** | Trademark and patent status | |
| **3** | Letter to guarantee product quality | |
| **4** | Package insert and labels | |
| **5** | Manufacturing process SOP or batch records | |
| **6** | Certificate of analysis, test methods for main ingredients | 2 copies |
| **8** | Specifications and method of analysis for finished product | 2 copies |
| **9** | Stability test and report | Including protocol |
| **10** | Free Sale Certificate | From US FDA; notarized |
| **11** | Authorization letter | |
| **12** | GMP Certificate | Notarized |
| **13** | Validation of aseptic operation | Depends on product |
| **14** | Sample for testing | |
| **15** | Registration fee | NT 10,000 (US $300) |

Attachment Form 1:

## Orphan Drug Application Requirements

**附表一、罕見疾病藥物查驗登記應檢附資料**

| 應檢送資料 | 罕見疾病藥品 | |
|---|---|---|
| | 國產 | 輸入 |
| 規費 | ○ | ○ |
| 藥品查驗登記申請書正、副本 | ○ | ○ |
| 有關品名商標專利等規定之切結書(甲) | ○ | ○ |
| 有關檢驗不合格等規定之切結書(乙) | ○ | ○ |
| 仿單標籤粘貼表二份 | ○ | ○ |
| 證照粘貼表 | ○ | ○ |
| 製造管制標準書或批次製造紀錄 | ○ | ○ |
| 主成分檢驗規格與方法及成績書二份 | ○ | ○ |
| 賦形劑檢驗規格與方法及成績書二份 | | △ |
| 成/產品檢驗規格與方法及成績書二份 | ○ | ○ |
| 安定性試驗書面作業程序及其檢驗報告 | ○ | ○ |
| 採用證明 | | |
| 原產國製售證明 | △ | ○ |
| 委託書 | | ○ |
| 藥品處方依據/醫療器材規格依據 | △ | |
| 藥品 GMP 後續查廠最近一次核准函影本/醫療器材 GMP 認可登錄證明函影本 | ○ | |
| 製造場所符合優良藥品製造規範證明 | | ○ |
| 無菌製劑確效書面報告三份 | | △ |
| 醫療器材依產品特性，檢附相關之物理、化學、生物相容或電學等技術性資料。 | | |
| 療效、品質及安全性資料 | 見附表二 | |
| 醫療器材臨床試驗報告書（至少需三篇且附其中文譯本） | | |
| 送驗 | ○ | ○ |

○ 表示附該項目之資料，　△表示視個案而定

Attachment Form 2:

Orphan Drug Application Additional Information

# 附表二 罕見疾病藥品查驗登記應檢附之療效、品質、安全性資料

| | | | 起源、發現經過、國外使用情形 | | | 物化性質、檢驗方法、規格 | | | 安定性試驗報告 | 安全性試驗報告 | | | | | | | | | 藥理作用 | | 吸收、分佈、代謝，排泄生體可用率/生體等性試驗報告 | | | | | | 安全性試驗報告 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 起源發現經過 | 國外使用情形 | 性質比較 | 構造式 | 物理化學性質 | 檢驗規格方法 | | 急性毒性 | 亞急性毒性 | 慢性毒性 | 胚胎試驗 | 依賴性 | 抗原性 | 變異原性 | 致癌性 | 局部刺激性 | 有效性證明 | 一般藥理 | 吸收 | 分佈 | 代謝 | 排泄 | 生體可用率 | 生體相等性 | 臨床試驗 | 醫學期刊 |
| 新成分 | | | ○ | Δ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | Δ | Δ | Δ | Δ | Δ | Δ | Δ | ○ | ○ | Δ | Δ | Δ | Δ | Δ | Δ | ○ | ○ |
| 同類藥物 | 新投與途徑 | | ○ | Δ | ○ | ╳ | ╳ | ○ | ○ | ○ | ○ | Δ | Δ | ╳ | ╳ | ╳ | ╳ | ╳ | ○ | ╳ | Δ | Δ | Δ | Δ | ○ | ╳ | ○ | ○ |
| | 新療效 | | ○ | Δ | ○ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ○ | ╳ | Δ | Δ | Δ | Δ | Δ | ╳ | ○ | ○ |
| | 新複方 | | ○ | Δ | ○ | ╳ | ╳ | ○ | ○ | ○ | ○ | Δ | ╳ | ╳ | ╳ | ╳ | ╳ | Δ | ○ | ○ | Δ | Δ | Δ | Δ | ○ | ╳ | ○ | Δ |
| | 新劑型 | 控釋製 | ○ | Δ | ○ | ╳ | ╳ | ○ | ○ | Δ | Δ | Δ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ○ | ╳ | ○ | Δ |
| | | 速放製 | ○ | Δ | ○ | ╳ | ╳ | ○ | ○ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ◎ | ◎ | ◎ | Δ |
| | 新使用劑量 | | ○ | Δ | ○ | ╳ | ╳ | ╳ | ╳ | Δ | Δ | Δ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ○ | ╳ | Δ | Δ | Δ | Δ | Δ | ╳ | ○ | Δ |
| | 新單位含量 | | ○ | Δ | ○ | ╳ | ╳ | ○ | ○ | Δ | Δ | Δ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | Δ | ╳ | ╳ | ╳ | ╳ | ╳ | ◎ | ◎ | ◎ | ╳ |
| | 疫苗 | | ○ | Δ | ○ | ╳ | ╳ | ○ | ○ | Δ | Δ | Δ | ╳ | ╳ | ○ | Δ | ╳ | Δ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ╳ | ○ | ○ |

註：○表示須檢附該項目之資料。

◎表示依下述方法擇一辦理：

(1) 生體相等性試驗。(2)生體可用率及臨床試驗。

╳表示不須檢附該項目之資料。

Δ表示視個案而定。

### 6.4.4 Orphan Drug Availability and Reimbursement Issues

The ability for patients to quickly obtain medication for a rare disease is still an issue in Taiwan. Conditions classified as "rare diseases" under the *Rare Disease Prevention and Medicine Law* entitle a patient to full financial coverage for medication and treatment.

Since many orphan drugs are very expensive, hospitals do not provide the drugs without prior reimbursement approval from the National Health Insurance Administration (NHIA). The MOHW has an approved list of orphan drugs to treat rare diseases. For orphan drugs that are not listed on this list, a special application for insurance reimbursement may be made.

The NHIA requires 4.5 working days to review a patient's diagnosis report before granting reimbursement for any drugs. In some cases, the NHIA can reimburse for drugs that are still in clinical trials.

It should be noted that the Taiwanese government has been very generous with respect to reimbursement for a variety of rare diseases. There are many patient or parent groups that have successfully lobbied the Taiwanese government for such monies. As a result, reimbursement levels have been very reasonable and oftentimes cover the entire cost of the medication and office visits. Over two-thirds of drugs with orphan drug designation have been included in National Health Insurance's reimbursement list since 2002.

## 6.5 HEALTH AUTHORITY CONTACT INFORMATION

Ministry of Health and Welfare (MOHW)
Address: No.36 Tacheng St., Datong District, Taipei, Taiwan 10341
Phone: +886-2-8590-6666
Fax: +886-2-2397-1548
Website: http://www.mohw.gov.tw/EN/Ministry/Index.aspx

Taiwan Food and Drug Administration (TFDA)
Address: No.161-2, Kunyang St., Nangang District, Taipei, Taiwan 115-61
Phone +886-2-2787-8000; +886-2-2787-8099
Website: http://www.fda.gov.tw/EN/index.aspx

Center for Drug Evaluation (CDE)
Address: 3F, No. 465, Sec. 6, Zhongxiao E. Road, Taipei, Taiwan 11557
Phone: +886-2-8170-6000
Fax: +886-2-8170-6001; +886-2-8170-6002
Website: http://www.cde.org.tw/English/Pages/e-default.aspx

## 6.6 ORPHAN DRUG ASSOCIATIONS

Taiwan Foundation for Rare Disorders
Address: 6F No.20 Changchun Road, Zhongshan District, Taipei, Taiwan 104
Phone: +886-2-2521-0717
Fax: +886-2-2567-3560
Email: rp02@tfrd.org.tw
Website: http://www.tfrd.org.tw/english

*In 1999, the Taiwan Foundation for Rare Disorders (TFRD) was established to identify and assist rare disease patients with medical treatment in Taiwan. TFRD places a large focus on patient and doctor support in order to improve the awareness of rare diseases in Taiwan. TFRD works with existing rare disease associations and sponsors activities in conjunction with these groups. It also helps to create new groups and organizations for rare diseases without group support.*

Taiwan Organization for Disadvantaged Patients
Phone: +886-2-2560-4501
Fax: +886-2-2523-0936
Website: (*in Chinese only*)
http://www.rare.org.tw/_sam0/intro.php?kind_id=15&web_name=TODP

*The TODP is a group made up of rare disease patients, patients' families, and patient groups, dedicated to providing disadvantaged rare disease patients with mutual support, exchange of experiences in medical care and relevant information.*

Taiwan Human Genetics Society
Address: No.128 Sec. Biomedical 100B Academy Road, Nankang District, Taipei, Taiwan 115
Phone: +886-2-2782-3770
Fax: +886-2-2789-0775
Email: thgs@genes-at-taiwan.com.tw
Website: http://www.genes-at-taiwan.com.tw (*in Chinese only*)

## 6.7 ORPHAN DRUGS APPROVED IN TAIWAN

附件三

### 附表二、行政院衛生署公告罕見疾病藥物名單

| 罕見疾病藥物名單　　中華民國99年3月1日 署授食字第0991601856號公告 | | | | | | | |
|---|---|---|---|---|---|---|---|
| 認定日期: 公告列入罕見疾病藥物名單中; 許可日期: 核發許可證,准予上市日期 | | | | | | | |
| 序號 | 成分名 | 劑型、劑量 | 適應症 | 認定日期 | 許可日期 | 聯絡單位 | 修正說明 |
| (一) | (RS)-2,3-bis (sulphanyl) propane-1-sulfonic acid (DMPS), sodium salt, Monohydrate | 〔Injection〕 | 急性汞中毒解毒劑 | 90年8月15日衛署藥字第0900055243號公告 | 90年12月10日 罕藥輸字第000003號 | 科懋生物科技股份有限公司 | |
| (二) | (RS)-2,3-Dimercapto-1-propanesulfonic acid (DMPS), sodium salt, Monohydrate | 〔Capsule〕 | 急慢性汞中毒（金屬汞，揮發性有機或無機化合物）慢性鉛中毒 | 90年8月15日衛署藥字第0900055243號公告 | 90年12月10日 罕藥輸字第000002號 | 科懋生物科技股份有限公司 | |
| (三) | [Meso-2,3-dimercaptosuccinic acid, DMSA] | 〔Capsule〕〔100 mg〕 | 鉛、砷、汞中毒之解毒 | 88年6月17日衛署藥字第88036149號公告 97年1月22日衛署藥字第0970302902號公告修正適應症 | 97年1月2日 罕藥製字第000011號 | 科進製藥科技股份有限公司 | |
| (四) | Agalsidase-alpha | 〔Injection〕 | alpha-galactosidase A deficiency (Fabry disease) | 91年4月9日衛署藥字第0910027540號公告 | 93年4月26日 罕菌疫輸字第000004 | 科懋生物科技股份有限公司 | |
| (五) | Agalsidase-beta | 〔Injection〕 | alpha-galactosidase A deficiency (Fabry disease) | 91年4月9日衛署藥字第0910027540號公告 | 93年4月26日 罕菌疫輸字第000005 | 吉帝藥品股份有限公司 | |
| (六) | Albendazole | 〔Tablet〕〔200 mg〕 | 鉤蟲感染之表皮幼蟲移行症 | 88年12月9日衛署藥字第88073234號公告 | | | |
| (七) | alpha 1-antitrypsin | injection | 原發性alpha 1-antitrypsin缺乏之肺氣腫患者的替代治療 | 94年1月28日衛署藥字第0940304588號公告 | | 海喬國際股份有限公司 | |
| (八) | alpha-glucosidase | injection | 龐貝氏症 | 94年1月28日衛署藥字第0940304588號公告 | | 昆泰股份有限公司 | |
| (九) | Ambrisentan | 5 mg and 10 mg tablet | 原發性肺高血壓 | 98年5月4日衛署藥字第0980305278號公告 | | 荷商葛蘭素史克藥廠股份有限公司台灣分公司 | |
| (十) | Anagrelide | 〔Capsule〕〔0.5 mg; 1.0 mg〕 | 原發性血小板過多症 | 88年6月17日衛署藥字第88036149號公告 | 92年5月21日 罕藥輸字第000007號 | 吉泰藥品股份有限公司 | |
| (十一) | Antivenin of Vipera Russelli | 〔Injection〕 | 鎖鏈蛇咬傷 | 91年11月14日衛署藥字第0910073830號公告 | 97年8月1日 罕菌疫製字第000001號 | 疾病管制局 | |

| 序號 | 成分名 | 劑型、劑量 | 適應症 | 認定日期 | 許可日期 | 聯絡單位 | 修正說明 |
|---|---|---|---|---|---|---|---|
| (十二) | Arginine | 〔Injection〕〔10 gm/100ml〕 | 尿素循環障礙 | 88年6月17日衛署藥字第88036149號公告 | | | |
| (十三) | Arsenic Trioxide | 〔Injection〕〔1 mg/ml, 10 ml/vial〕 | 急性前骨髓細胞白血病 | 88年12月9日衛署藥字第88073234號公告 | 91年2月5日<br>罕藥製字第000005號 | 台灣東洋藥品股份有限公司 | |
| (十四) | Artemisinin | 〔Tablet〕〔100 mg〕 | 瘧疾 | 88年12月9日衛署藥字第88073234號公告<br>98年5月4日衛署藥字第0980305278號公告修正適應症 | | | |
| (十五) | Atovaquone-proguanil | 〔Tablet〕〔250 mg+100 mg〕 | 瘧疾 | 88年12月9日衛署藥字第88073234號公告 | | | |
| (十六) | Betaine | 〔Powder for Reconstitution〕〔1 gm/scoopful | 高胱氨酸尿症 | 88年6月17日衛署藥字第88036149號公告 | | | |
| (十七) | Bosentan | 62.5 and 125 mg tablet | 原發性肺動脈高血壓 | 92年11月18日衛署藥字第0920331943號公告 (95年8月22日衛署藥字第0950325795號公告修 | 94年7月26日<br>罕藥輸字第000012號 (62.5 mg)<br>罕藥輸字第000013號 (125 mg) | 科懋生物科技股份有限公司 | |
| (十八) | Citrulline | 〔Tablet, 600 mg〕〔oral solution, 1 g/10 ml〕 | 先天性因 citrulline缺乏引起尿素代謝異常之高血氨症 | 89年8月1日衛署藥字第0890009615號公告 (92年5月2日衛署藥字第0920305496號公告新增oral solution劑型) | 90年12月11日<br>罕藥輸字第000001號 | 科懋生物科技股份有限公司 | |
| (十九) | Cysteamine Bitartrate | 〔Capsule〕〔EQ 50 mg, 150 mg Base | nephropathic cystinosis | 88年12月9日衛署藥字第88073234號公告 | | | |
| (二十) | Dantrolene | (Injection)〔20 mg/vial〕 | 惡性高溫熱 | 88年12月9日衛署藥字第88073234號公告 | | | |

| 序號 | 成分名 | 劑型、劑量 | 適應症 | 認定日期 | 許可日期 | 聯絡單位 | 修正說明 |
|---|---|---|---|---|---|---|---|
| (二十一) | Deferiprone (Kelfer) | 〔Capsule〕〔250 mg；500 mg〕 | 重型海洋性貧血(Thalassemia major)病人，使用Deferrioxamine治療不理想或無法接受時;或在醫師嚴格監測不良反應(如:白血球數目,肝功能狀況…)下,與Deferrioxamine合 | 90年5月21日衛署藥字第0900032249號公告 | 91年2月25日罕藥輸字第000004號(250 mg)<br>罕藥輸字第000005號(500 mg) | 康寧藥業股份有限公司 | |
| (二十二) | Diazoxide | 〔Capsule, Suspension〕〔50 mg; 50 mg/ml〕 | persistent hyperinsulinemic hypoglycemia of infancy (PHHI) | 88年12月9日衛署藥字第88073234號公告<br>(92年11月18日衛署藥字第0920331943號公告修正適應症) | | | |
| (二十三) | Diloxanide Furoate | 〔Tablet〕〔500 mg〕 | 痢疾阿米巴帶原者 | 88年12月9日衛署藥字第88073234號公告 | | | |
| (二十四) | Dimercaprol | 〔Injection〕〔10%〕 | 重金屬解毒劑 | 88年12月9日衛署藥字第88073234號公告 | | | |
| (二十五) | Epoprostenol | 〔Injection〕〔0.5 mg base/vial; 1.5 mg base/vial〕 | 原發性肺高血壓 | 88年6月17日衛署藥字第88036149號公告<br>(91年11月14日衛署藥字第0910073830號公告修正適應症) | | | |
| (二十六) | Gabapentin | 〔Capsule; Tablet〕〔600 mg, 800 | 脊髓側索硬化症(Amyotrophic Laterol Sclerosis ALS) | 88年12月9日衛署藥字第88073234號公告 | | 派德股份有限公司 | |
| (二十七) | Galsulfase | 〔Injection〕〔5.0 mg/vial〕 | 黏多醣症第6型 Mucopolysaccharidosis VI | 95年1月25日衛署藥字第0950302125號公告 | | | |
| (二十八) | Glatiramer acetate | 〔Injection〕〔20 mg/vial〕 | 多發性硬化症(Multiple Sclerosis) | 88年12月9日衛署藥字第88073234號公告 | 94年3月9日罕藥輸字第000009號(powder for solution for injection)<br>95年12月21日罕藥輸字第000015號(solution for injection) | 海喬國際股份有限公司 | |

| 序號 | 成分名 | 劑型、劑量 | 適應症 | 認定日期 | 許可日期 | 聯絡單位 | 修正說明 |
|---|---|---|---|---|---|---|---|
| (二十九) | Hemin | 〔Injection〕 | 紫質症 | 88年6月17日衛署藥字第88036149號公告 | | | |
| (三十) | idursulfase (iduronate-2-sulfatase) | | long term enzyme replacement therapy for patients with MPS II (Hunter Syndrome) | 95年8月22日衛署藥字第0950325795號公告 | | | |
| (三十一) | Iloprost | nebuliser solution solution for infusion | 原發性肺高血壓 | 91年8月8日衛署藥字第0910049668號公告(nebuliser solution)<br>98年5月4日衛署藥字第0980305278號公告(solution for infusion) | 94年5月23日<br>罕藥輸字第000011號(nebuliser solution) | 台灣拜耳股份有限公司 | |
| (三十二) | Imiglucerase | 〔Injection〕〔200 units/vial〕 | 第一型(Type I)高雪氏症 | 88年6月17日衛署藥字第88036149號公告 | 94年11月3日<br>罕菌疫輸字第000006號 | 吉帝藥品股份有限公司 | |
| (三十三) | Interferon-Beta-1a | 〔Injection〕〔3MIU、6MIU、12MIU/vial〕 | 多發性硬化症(Multiple Sclerosis) | 88年12月9日衛署藥字第88073234號公告 | 90年6月6日<br>罕菌疫輸字第000001號<br>90年11月26日 | 新加坡雪蘭諾股份有限公司台灣分公司 | |
| (三十四) | Interferon-Gamma 1b | 〔Injection〕〔100 mcg/0.5ml〕 | 慢性肉芽腫病(Chronic Granulomatous Disease) | 88年12月9日衛署藥字第88073234號公告 | | | |
| (三十五) | Iodoquinol | 〔Tablet〕〔210mg; 650 mg〕 | 阿米巴性痢疾 | 88年12月9日衛署藥字第88073234號公告<br>98年5月4日衛署藥字第0980305278號公告修正適應症 | | | |
| (三十六) | Ivermectin | 〔Tablet〕〔3 and 6 mg〕 | 糞小桿線蟲感染、血絲蟲感染 | 88年12月9日衛署藥字第88073234號公告<br>98年5月4日衛署藥字第0980305278號公告新增劑量 | | | |

| 序號 | 成分名 | 劑型、劑量 | 適應症 | 認定日期 | 許可日期 | 聯絡單位 | 修正說明 |
|---|---|---|---|---|---|---|---|
| (三十七) | L-5-hydroxytryptophan (5-HTP) | 〔Capsule〕 | BH4缺乏性苯酮尿症 (異型苯酮尿症)〔Tetrahydrobiopterin (BH4) deficiency PKU〕 | 90年8月15日衛署藥字第0900055243號公告 | | | |
| (三十八) | Lactic acid bacteria | oral use | chronic pouchitis disease 慢性囊炎疾病 | 91年8月8日衛署藥字第0910049668號公告 | | 翰亨實業股份有限公司 | |
| (三十九) | Laronidase | 100 units/ml solution for infusion | 黏多醣儲積症第一型 | 92年11月 18日衛署藥字第0920331943號公告 | 95年9月13日<br>罕菌疫輸字第000007號<br>罕菌疫輸字第000008號 | 吉帝藥品股份有限公司 | |
| (四十) | Levocarnitine | 〔Injection; Oral Solution; Tablet〕[200 mg/ml, 1 gm/10ml, 330 mg, 1gm] | 用於先天遺傳性代謝異常的續發性Carnitine缺乏症病患之急性慢性治療 | 88年6月17日衛署藥字第88036149號公告 | 91年5月3日<br>罕藥輸字第000006號(tab) | 健康化學製藥股份有限公司(i)翰亨實業股份有限公司(t) | |
| (四十一) | miglustat | capsule | Type I Gaucher Disease<br>Niemann-Pick Disease Type C | 94年1月28日衛署藥字第0940304588號公告(Type I Gaucher Disease)<br>98年5月4日衛署藥字第0980305278號公告(Niemann-Pick Disease Type C) | | 科懋生物科技股份有限公司 | |
| (四十二) | Mitotane | 〔Tablet〕〔500 mg〕 | 腎上腺皮質癌 | 88年12月9日衛署藥字第88073234號公告 | | | |
| (四十三) | Modafinil | 200 mg | 改善猝睡症患者的日間過度睡眠症狀 | 90年5月21日衛署藥字第0900032249號公告(95年1月25日衛署藥字第0950302125號公告修正適應症) | 94年2月24日<br>罕藥輸字第000010號 | 信東生技股份有限公司 | |
| (四十四) | Natalizumab | 300 mg/15 ml vial, solution for infusion | 多發性硬化症 | 98年5月4日衛署藥字第0980305278號公告 | | | |

| 序號 | 成分名 | 劑型、劑量 | 適應症 | 認定日期 | 許可日期 | 聯絡單位 | 修正說明 |
|---|---|---|---|---|---|---|---|
| (四十五) | Nitisinone | 2.0 mg/cap | 酪胺酸血症第一型 Tyrosinemia type I | 95年1月25日衛署藥字第0950302125號公告 | | | |
| (四十六) | Nitric Oxide | 〔Inhaler〕 | 新生兒原發性肺高血壓用 | 88年6月17日衛署藥字第88036149號公告 | | | |
| (四十七) | Paromomycin Sulfate | 〔Capsule〕〔250 mg〕 | 隱孢子蟲感染、阿米巴性痢疾 | 88年12月9日衛署藥字第88073234號公告<br>98年5月4日衛署藥字第0980305278號公告修正適應症 | | | |
| (四十八) | Phenytoin | 〔 Capsule 〕〔30 mg〕 | 癲癇症(限用於調整劑量) | 88年12月9日衛署藥字第88073234號公告 | | | |
| (四十九) | Phosphate solution | 〔Solution〕 | 性聯遺傳型低磷酸鹽性佝僂症 [X-linked hypophospatemic Rickets] | 90年8月15日衛署藥字第0900055243號公告 | | | |
| (五十) | potassium acid phosphate + sodium acid phosphate, anhydrous | 〔Tablet〕 | 性聯遺傳型低磷酸鹽性佝僂症 [X-linked hypophospatemic Rickets] | 91年11月14日衛署藥字第0910073830號公告 | | 吉帝藥品有限公司 | |
| (五十一) | Primaquine-Phosphate | 〔Tablet〕〔7.5 mg〕 | 瘧疾、肺囊蟲肺炎 | 88年12月9日衛署藥字第88073234號公告<br>98年5月4日衛署藥字第0980305278號公告修正劑量及適應症 | | | |
| (五十二) | protein C | injection | 先天性protein C缺乏所致之嚴重靜脈血栓 | 94年1月日衛署藥字第0940304588號公告 | | 海喬國際股份有限公司 | |
| (五十三) | Pyrimethamine | 〔Tablet〕〔25 mg〕 | 弓形蟲感染 | 88年12月9日衛署藥字第88073234號公告<br>98年5月4日衛署藥字第0980305278號公告修正成分及劑量 | | | |
| (五十四) | mefloquine | 〔Tablet〕〔250 mg〕 | 瘧疾 | 88年12月9日衛署藥字第88073234號公告<br>98年5月4日衛署藥字第0980305278號公告修正成分劑量及適應症 | | | |

| 序號 | 成分名 | 劑型、劑量 | 適應症 | 認定日期 | 許可日期 | 聯絡單位 | 修正說明 |
|---|---|---|---|---|---|---|---|
| (五十五) | Recombinant human insulin-like growth factor 1, rhIGF-1 | | Laron Syndrome | 95年8月22日衛署藥字第0950325795號公告 | 97年3月17日罕菌疫輸字第000009號 | 吉帝藥品股份有限公司 | |
| (五十六) | Risedronate | 〔Tablet〕〔30 mg〕 | 原發性變形性骨炎（Primary Paget disease） | 90年3月22日衛署藥字第0900018284號公告 | 92年8月21日罕藥輸字第000008號 | 台灣安萬特藥品股份有限公司 | |
| (五十七) | Sacrosidase | 〔Oral Solution〕〔900 IU/ml〕 | PKU with congenital sucrase-isomaltase deficiency | 88年12月9日衛署藥字第88073234號公告 | | | |
| （五十八） | Sildenafil citrate | 〔Tablet〕〔20 mg〕 | 原發性肺高血壓 | 98年5月4日衛署藥字第0980305278號公告 | | 輝瑞大藥廠股份有限公司 | |
| (五十九) | Sod. Benzoate | 〔Capsule〕[250 mg] | Non-ketotic hyperglycinemia | 88年6月17日衛署藥字第88036149號公告 | 90年3月21日罕藥製字第000001號 | 科進製藥科技股份有限公司 | |
| (六十) | Sodium phenylacetate and sodium benzoate | injection | 先天性尿素循環代謝障礙 | 96年8月8日衛署藥字第0960303535號公告 | | 吉發企業股份有限公司 | |
| (六十一) | Sodium Phenylbutyrate | [Powder; Tablet] [3 gm /teaspoonful; 500 mg] | 缺乏carbamylphosphate synthetase (CPS), Ornithine transcarbamylase (OTC)或Argininosuccinic synthetase (AS)之先天性尿素循環障 | 88年6月17日 衛署藥字第88036149號公告(97年1月22日衛署藥字第0970302902號公告修正適應症) | | | |
| (六十二) | Sodium Stibogluconat | 〔Injection〕〔100 mg/ml, 100 ml/bot〕 | 利什曼症(黑熱病) | 88年12月9日衛署藥字第88073234號公告 | | | |
| (六十三) | taltirelin hydrate | 〔Tablet〕 | 脊髓小腦變性症 spinocerebellar degeneration, SCD | 97年1月22日衛署藥字第0970302902號公告 | | 台田藥品股份有限公司 | 一、 本品項刪除。<br>二、 本品適應症應修正為「脊髓小腦退化性動作協調障礙 spinocerebellar ataxia, SCA」，惟因廠商未提供足夠資料證明其適用之疾病分型，無法據以認定，故予以刪除。 |
| (六十四) | tetrabenazine | 〔Tablet〕 | 亨汀頓氏舞蹈症 Huntington disease | 97年1月22日衛署藥字第0970302902號公告 | | | |

| 序號 | 成分名 | 劑型、劑量 | 適應症 | 認定日期 | 許可日期 | 聯絡單位 | 修正說明 |
|---|---|---|---|---|---|---|---|
| (六十五) | Tetrahydro-Biopterin(BH4) | 〔Tablet〕〔10, 50 and 100 mg〕 | Treatment of patients with hyperphenylalaninemia due to tetrahydrobiopterin deficiency. Tetrahydrobiopterin-responsive | 88年12月9日衛署藥字第88073234號公告<br>98年5月4日衛署藥字第0980305278號公告修正劑量及適應症 | | | |
| (六十六) | Thalidomide | 〔Capsule〕〔50 mg〕 | 結節狀紅斑leprosum | 88年12月9日衛署藥字第88073234號公告 | 91年10月16日罕藥製字第000006號 | 台灣東洋藥品股份有限公司 | |
| (六十七) | Thymosin alfa 1 | injection | DiGeorge Syndrome | 91年8月8日衛署藥字第0910049668號公告 | | | |
| (六十八) | Thyrotropin alfa Injection | [Injection] [1.1mg/ml] | 甲狀腺分化癌治療之輔助診斷製劑 | 88年6月17日衛署藥字第88036149號公告 | 92年5月6日罕菌疫輸字第000003 | 吉帝藥品股份有限公司 | |
| (六十九) | Tobramycin | 300 mg/5 ml solution for inhalation | 囊狀纖維化症患者因基因缺陷致肺部因綠膿桿菌慢性感染,造成反覆急性發作支氣管擴張症之持續性治療 | 95年8月22日衛署藥字第0950325795號公告 | | | |
| (七十) | TPN for PKU with congenital sucrase-somaltase deficiency之全靜脈營養注射 | 〔Injection〕 | TPN For PKU with congenital sucrase-isomaltase deficiency之全靜脈營養注射劑 | 88年12月9日衛署藥字第88073234號公告 | | | |
| (七十一) | treprostinil sodium | 〔Injection〕〔1.0, 2.5, 5.0, 10.0 | 原發性肺高血壓 | 91年11月 14日衛署藥字第0910073830號公告 | | 科懋生物科技股份有限公司 | |
| (七十二) | Tretinoin | soft gelatin capsules 10 | 急性前骨髓性白血病 | 92年11月 18日衛署藥字第0920331943號公 | | 羅氏大藥廠股份有限公司 | |
| (七十三) | Trientine HCl | [Capsule] [250, 300 mg] | 威爾森氏病(Wilson Disease) | 88年6月17日衛署藥字第88036149號公告<br>97年7月9日衛署藥字第0970305564號公告新增劑量 | | | |
| (七十四) | Zinc Acetate | [Capsule] [25-50 mg] | 威爾森氏病(Wilson Disease) | 90年12月4日衛署藥字第0900074831號公告 | 93年11月29日罕藥製字第000007號(50 mg, 科進)<br>95年1月26日罕藥製字第000010號(25 mg, 科進)<br>94年3月15日罕藥製字第000008號(25 mg, 吉帝)<br>94年3月15日罕藥製字第000009號(50 mg, 吉帝) | 科進製藥科技股份有限公司<br>吉帝藥品股份有限公司 | |

# 7. KOREA

## 7.1 OVERVIEW

The Korean pharmaceutical market is currently valued at around $15 billion, the fourth largest in Asia behind those of Japan, China, and India. While the market has been growing steadily at 7-9% per year for the past several years, the Ministry of Food and Drug Safety (MFDS) continues to work on the internationalization and improvement of the country's pharmaceutical regulations. In May 2005, the Korean government entered into a Memorandum of Understanding with the World Health Organization to participate in an International Program on Chemical Safety for pharmaceuticals and other medical products. Some of the departments under the MFDS and their respective duties include the following:

- Pharmaceutical Safety Bureau
    - Develops safety plans for drugs, cosmetics and medical devices
- Safety Evaluation Office
    - Controls the safety standards for drugs, devices and foods
- National Institute of Toxicological Research
    - Reviews safety and efficacy data submitted by drug registration applicants
- Regional Agencies
    - Agencies that conduct drug/food laboratory inspections and surveillance

## 7.2 DRUG REGISTRATION OVERVIEW

The *Guideline to Registration of Drug Substances* (Notification No. 2002-20) became effective March 25, 2004. This guideline outlines the basic drug registration process, including data preparation, the scope of the data required and possible exemptions from submission.

The registration of new chemical entities in Korea requires the completion of the *Application Form for Registration of Drug Substances*. The required items are as follows:

- Name, address and contact information of manufacturer
- Manufacturer's registration number
- Information on manufacturer's representative, including email address
- Conformity with Korea Good Manufacturing Practice, or other recognized GMP standards (i.e. US FDA GMP)
- Product trade name and generic name
- Product appearance, physical and chemical properties, and route of administration
- Manufacturing process and quality control measures
- Stability information
- Packaging, containers and product handling information
- Batch analysis, analytical procedures and solvents used
- Drug samples for quality testing

- Storage and shelf life

If any of the above information is written in a language other than Korean, the original foreign language document should be submitted along with a summary in Korean. If necessary, the MFDS may request that a full translation of the information be made. Generally, the application review process by the MFDS takes approximately 120 days to complete. In the case of imported drugs, the MFDS may call for an inspection of the foreign manufacturing site; the applicant is notified of an inspection 20 days prior to the inspection.

## 7.3 ORPHAN DRUGS IN KOREA

### 7.3.1 Orphan Drug Definition and Legislation

In Korea, orphan drugs are supplied to patients by pharmaceutical companies or the Korea Orphan Drug Center. In 2010, the Korean government targeted 132 rare diseases for free medical care to patients family's monthly income is less than $3,600 (KRW 4 million) and with assets totaling less than $180,000 (KRW 200 million). Currently, 184 orphan drugs had been approved by the KFDA.

The requirements for orphan drug designation in Korea are as follows:

- Fewer than 20,000 people in Korea suffer from the disease/condition, or there is no available treatment for the disease/condition in Korea.
- If the product is manufactured in Korea, the total production should be less than 5 billion won (US$5 million). If the drug is manufactured outside of Korea and imported for sale, the total imports of the drug should be less than US$5 million.

The orphan drug application process takes around 6 to 9 months to complete. Approved orphan drugs are generally granted about 6 years of marketing exclusivity, at the government's discretion. Applications for orphan drugs may be subject to a 50% price reduction from the normal drug application fee.

In general, Korea has reimbursed orphan drugs at about one-half to two-thirds of the actual cost of the drug and doctor visits. Patient and parent groups have also lobbied the Korean government with some success. In some cases, though, reimbursement levels are too low for drugmakers. Shire Human Genetic Therapies tried negotiating with Korea's National Health Insurance Corporation for higher reimbursement before it would sell Elaprase, a treatment for Hunter syndrome, into Korea. The drug was approved for sale in 2008. The NHIC determines reimbursement for orphan drugs on a case-by-case basis and is strongly oriented toward keeping overall medical spending down.

### 7.3.2 Korea's Orphan Drug Application Requirements

| | Required Documents and Information | Details |
|---|---|---|
| **1** | Manufacturing Certificate and Free Sales Certificate (FSC) or Certificate for Pharmaceutical Product (CPP) | Include manufacturer name and address and complete qualitative composition, including excipient specifications |
| **2** | Product specifications: formulation, indications, contraindications, regimen, side effects, shelf-life, etc. | |
| **3** | GMP Certificate | Notarized |
| **4** | Origin, discovery and development history | |
| **5** | Product structure, chemical and biological properties | |
| **6** | Manufacturing process | |
| **7** | Validated specifications and test methods for three lots | Test results from local importer and foreign manufacturing company. Local importer results can be omitted if importer has demonstrated KGMP compliance. |
| **8** | Stability test reports | For three lots |
| **9** | Toxicology study reports for:<br>Single dose toxicity<br>Repeated dose toxicity<br>Reproduction toxicity<br>Genotoxicity<br>Immunotoxicity | Should meet Good Laboratory Practice regulations |
| **10** | Pharmacology study reports, including general pharmacology, efficacy and pharmacokinetics (ADME) | Published in SCI Journal; or as a report submitted and reviewed by a regulatory authority for pre-market approval |
| **11** | Clinical reports for Phase I, II and III trials | Published in SCI Journal; or as a report submitted and reviewed by a regulatory authority for pre-market approval |
| **12** | List of countries where the product is already registered and sold; orphan drug status in other countries | Include authorized prescribing information from the official drug book (PDR, Rote Liste, etc.). |
| **13** | Product brochure or other literature | |
| **14** | Orphan Drug Recommendation Form from a doctor from the Korean Hospital Association or South Korea Orphan Drug Center | Recommendation is not necessary for orphan drugs that are pre-designated in other countries |

**Orphan Drug Designation Application Form (Form 1 No. 6)**
(Submit to the Commissioner of the Korea Food and Drug Administration)

# Orphan Drug Application

| | | | |
|---|---|---|---|
| Manufacturer Name: | | Representatives | |
| Address: | | | |
| Name | | Contact Information | Phone:<br>Fax: |

| | |
|---|---|
| Product structure, chemical and biological properties | |
| Target diseases | |
| Product | |
| Manufacturer | |

"Regulation on Orphan" in accordance with the provisions of Article 3 designated orphan drug seeks to submit this form.

Year Month Day

Applicant (signature)

**Food and Drug Administration**

| Attachments to the application | Included (○, ×) |
|---|---|
| 1. Proof Documents for Orphan Drugs (refer to Regulations Article 3 Paragraph 1 No.) | |
| 2. Orphan Drug Recommendation (refer to regulations Article 3 Paragraph 2 No.) | |
| 3. Use of alternative materials for orphan drug specification form ( refer to Regulations Article 3 ) | |

210 ㎜ × 297 ㎜ [Plain Paper 60g / ㎡ (Recycled)]

Original Form

[별지 제1호서식]

# 희귀의약품 지정 신청서

| | | | | |
|---|---|---|---|---|
| 신청인 | 제조(영업)소 명 | | 대 표 자 | |
| | 제조(영업)소 소 재 지 | | | |
| | 성 명 | | 연 락 처 | 전화:<br>팩스: |
| 제 제 명 (주성분명, 함량 및 제형) | | | | |
| 대 상 질 환 | | | | |
| 제 품 명 | | | | |
| 제 조 원 | | | | |

「희귀의약품지정에관한규정」 제3조의 규정에 따라 희귀의약품으로 지정받고자 이 신청서를 제출합니다.

년 월 일

신청인 (서명 또는 인)

**식품의약품안전청장** 귀하

| 구비서류 | 첨부여부 (○,×) |
|---|---|
| 1. 희귀의약품에 해당함을 입증하는 서류(동 규정 제3조제1호) | |
| 2. 희귀의약품 지정추천서(동 규정 제3조제2호) | |
| 3. 희귀의약품 지정추천서 대체 자료(동 규정 제3조 단서) | |

210㎜×297㎜[일반용지 60g/㎡(재활용품)]

**Orphan Drug Recommendation Form (Appendix II No. 6)**

# Orphan Drug Recommendation Form

| | | | |
|---|---|---|---|
| Name | | Representatives | |
| Address | | | |
| Product structure, chemical and biological properties | | | |
| Target diseases | | | |
| Product | | Manufacturer | |

The orphan drug has successfully met the provisions for the recommendation process of the regulation

Year Month Day

Referral (signature)

**Food and Drug Administration**

Notes:

1. Recommendation and reason
2. Alternate medicines and procedures (including any relevant information)
3. Statistical data for targeted disease
4. Other notes and comments

210 ㎜ × 297 ㎜ [Plain Paper 60g / ㎡ (Recycled)]

Original Form:

[별지 제2호서식]

## 희귀의약품 지정 추천서

| | | | |
|---|---|---|---|
| 제 조 ( 영 업 ) 소 명 | | 대 표 자 | |
| 소 재 지 | | | |
| 제 제 명<br>(주성분명, 함량 및 제형) | | | |
| 대 상 질 환 | | | |
| 제 품 명 | | 제 조 원 | |

위 의약품이 「희귀의약품지정에관한규정」에서 정한 바에 따라 희귀의약품으로 지정할 필요가 있다고 판단되었기에 이를 추천합니다.

년 월 일

추천인 (서명 또는 인)

**식품의약품안전청장** 귀하

붙 임 : 1. 추천경위 및 사유
2. 대체의약품 또는 대체치료법에 대한 의약학적 견해 및 그 근거
3. 대상질환에 대한 통계자료(인구대비 발생비율등) 및 그 근거
4. 기타 참고의견

210㎜×297㎜[일반용지 60g/㎡(재활용품)]

## 7.4 HEALTH AUTHORITY CONTACT INFORMATION

Ministry of Health and Welfare
Address: 13 Duom 4-ro, Sejong, Korea 339-012
Phone: +82-2502-8272
Fax: +82-22110-6453
Email: webmaster@mohw.go.kr
Website: http://english.mohw.go.kr

Korea Food and Drug Administration
Osong Health Technology Administration Complex, 187 Osongsaengmyeong2(i)-ro, Osong-eup, Cheongwon-gun, Chungcheongbuk-do, Korea 363-700
Phone: +82-43-719-1564
Email: kfda@kfda.go.kr
Website: http://www.mfds.go.kr/eng/index.do

## 7.5 ORPHAN DRUG ASSOCIATIONS

Korea Orphan Drug Center
Address: Poonglim Building 9th floor, 823 Yoksam-dong, Gangnam-gu, Seoul, Korea 135-784
Phone: +82-2508-7316
Fax: +82-2508-7319
Email: admin@kodc.or.kr
Website: http://www.kodc.or.kr/english/about1.asp
*(English version rarely updated)*

*The KODC was established as a non-profit organization to improve rare disease treatment and improve the quality of life for rare disease patients in Korea. The Center maintains a database with information on rare diseases for patients and physicians and is able to import and distribute medications without MFDS permission for the treatment of rare disease.*

### 7.6 ORPHAN DRUGS APPROVED IN KOREA

The full list of Korea's orphan drug approvals (in Korean) can be obtained from http://www.kodc.or.kr/search/supplyutong.asp

The table below is a list of approved orphan drugs in Korea through October 2008.

| Approval | Generic Name | Trade Name | Indication | Company |
|---|---|---|---|---|
| 1/9/1993 | Protirelin | Relafact TRH | Diagnosis of thyroid gland and pituitary function. | Handok Pharmaceutical Co., Ltd. |
| 1/19/1993 | Anti-human lympho-cyte immune globuline (equine) | Lymphoglobuline | Prevention and treatment of rejection episodes in kidney, heart, pancreas and liver transplantation. | Woo Yang Pharmaceutical, Ltd. |
| 1/19/1993 | Anti-human thymocyte rabbit immunoglobulin | Thymoglobuline | Prevention and treatment of rejection episodes in kidney, heart, pancreas or liver transplantation. | Woo Yang Pharmaceutical, Ltd. |
| 1/27/1993 | Clodronate disodium tetrahydrate 374.84mg | Ostac injection | 1. Bone metastasis of the solid cancer (breast cancer, prostatic cancer, thyroid carcinoma, etc.); 2. Osteomalasia by hematological neoplasia (multi myeloma, etc.); 3. Cancer-related hypercalcemia by bone metastasis. | Chong Kun Dang Pharmaceutical Corp. |
| 2/1/1993 | Ubenimex | Bestatin capsule | To increase survival time of adult patients with acute non-lymphocyte leukemia by the combination of chemotherapy after a complete remission. | Dong-a Pharmaceutical Co., Ltd. |
| 2/24/1993 | Clodronate disodium tetrahydrate 499.79mg | Ostac capsule | 1. Bone metastasis of the solid cancer (breast cancer, prostatic cancer, thyroid carcinoma, etc.); 2. Osteomalasia by hematological neoplasia (multi myeloma, etc.); 3. Cancer-related hypercalcemia by bone metastasis. | Chong Kun Dang Pharmaceutical Corp. |
| 3/17/1993 | Peptides from tymus, equivalent to 200mg glandulae | Thymus AM | Deficient immunity of every kind (susceptibility to infection, chronic bacterial and virus diseases such as infections of the urinary tract, bronchitis, herpes and hepatitis). To increase immunity in the case of infectious processes, malignant neoplasms and precancerous stages. | Woo Yang Pharmaceutical, Ltd. |

| Approval | Generic Name | Trade Name | Indication | Company |
|---|---|---|---|---|
| 3/17/1993 | 200mg of the lyophilized thymus corresponding to 1g of fresh glands | Thymus AM Dragees | Deficient immunity of every kind (susceptibility to infection, chronic bacterial and virus diseases such as infections of the urinary tract, bronchitis, herpes and hepatitis). | Woo Yang Pharmaceutical, Ltd. |
| 3/19/1993 | L-Asparagainase | Leunase injection | Acute/chronic leukemia, malignant lymphoma. | Choong Wae Co., Ltd. |
| 4/8/1993 | Microfibrillar collagen hemostat (MCH) | Avitene flour | Hemostasis during surgery. | Nano Pharmaceutical Co., Ltd. |
| 4/8/1993 | Microfibrillar collagen hydrochloride | Avitene sheets (non woven web) | Hemostasis during surgery. | Nano Pharmaceutical Co., Ltd. |
| 5/1/1993 | Didanosine | Videx tablet 25mg, 100mg | Treatment of HIV-1 infection in combination with other antiretroviral agents. | BMS Korea Ltd. |
| 7/23/1993 | Teniposide | Vumon | Generalized malignant lymphomas (Phases III and IV), Hodgkin's disease, reticulosarcoma, lymphosarcoma, intracranial tumors, glioblastoma, astrocytoma, ependymona, urinary bladder tumors (in particular papillomatous forms). | Boryung Pharmaceutical Co., Ltd. |
| 7/24/1993 | Tetanus, diphtheria, streptococcus, tuberculin, proteus, candida, and trichophyton antigens; glycerin control | Multi-test | To estimate and diagnose positiveness and negativeness of tetanus, diphtheria, candida, proteus, tubercle bacillus, ringworm and favus. | Hanbul Pharmaceutical Co., Ltd. |
| 8/3/1993 | L-Asparaginase (Erwinia) 10,000 IU | Erwinase injection | Acute and chronic leukemia/malignant lymphoma. | Beaufour Ipsen Korea |
| 9/10/1993 | Muromonab CD3 | Orthoclone OKT3 injection | Treatment of acute allograft rejection in renal transplant patients. | Janssen Korea Ltd. |
| 10/28/1993 | Aqueous extract obtained from 1, 5, 10, 20, 30, 50mg of fresh plant Viscum album L. (Abietis) | Helixor A1, 5, 10, 20, 30, 50, 100mg injection | Additive treatment for all types of tumors; prevention of relapse (recurrence prophylaxis) following tumor surgery, radiation or chemotherapy for malignant diseases of the haematopoietic organs (leukemia, lymphoma, multiple myeloma); for stimulation of bone marrow function; for defined precancerous lesions. | Boryung Pharmaceutical Co., Ltd. |

| Approval | Generic Name | Trade Name | Indication | Company |
|---|---|---|---|---|
| 10/28/1993 | Aqueous extract obtained from 50mg of fresh plant Viscum album L. (Mali) | Helixor M1, 5, 10, 20, 30, 50, 100mg injection | Additive treatment for all types of tumors; prevention of relapse (recurrence prophylaxis) following tumor surgery, radiation or chemotherapy for malignant diseases of the haematopoietic organs (leukemia, lymphoma, multiple myeloma); stimulation of bone marrow function; defined precancerous lesions. | Boryung Pharmaceutical Co., Ltd. |
| 3/14/1994 | Dermatophagoides Pteronyswsinus, Dermatophagoides FarinePhenol 0.5% w/v (B.P) water for injections (Ph.Eur) Aluminum hydroxide | Alavac-S Complete course | Treatment of allergic diseases, e.g. allergic bronchial asthma, allergic rhinitis (hayfever). | Shin Kwang New Drugs Co., Ltd. |
| 3/14/1994 | Dermatophagoides Pteronyswsinus, Dermatophagoides FarinePhenol 0.5% w/v (B.P) water for injections (Ph.Eur) Aluminum hydroxide | Alavac-S Maintenance course | Treatment of Allergic diseases, e.g. allergic bronchial asthma, allergic rhinitis (hayfever) | Shin Kwang New Drugs Co., Ltd. |
| 3/18/1994 | Dipalmitoylphosphatid-ylcholine | Exosurf | Prophylaxis of respiratory distress syndrome (RDS) in premature infants with birthweight less than 1350g who have evidence of pulmonary immaturity; Rescure treatment of infants who have developed RDS. | Handok Pharmaceutical Co., Ltd. |
| 5/16/1994 | Imiglucerase | Cerezyme injection | Long-term enzyme replacement therapy in patients with a confirmed diagnosis of Type I Gaucher disease resulting in one or more of the following: anemia caused by any condition except iron deficiency, thrombocytopenia, bone disease caused by any condition except vitamin D deficiency, hepatomegaly or splenomegaly. | Sam-Oh Pharmaceutical Co., Ltd. |

| Approval | Generic Name | Trade Name | Indication | Company |
|---|---|---|---|---|
| 5/16/1994 | Allergen Extract | Comprehensive skin test cabinet | Diagnosis of allergic diseases, e.g. allergic bronchial asthma, allergic rhinitis (hayfever). | Shin Kwang New Drugs Co., Ltd. |
| 5/16/1994 | Allergen Extract | Diagnostic Allergen Extracts | Diagnosis of IgE-mediated allergic disease. | Shin Kwang New Drugs Co., Ltd. |
| 8/22/1994 | Zalcitabine | Hivid | Treatment of adult patients with advanced HIV infection (CD4 cell count < 300cells/mm3) who have demonstrated clinical or immunologic deterioration. | Roche Korea Co.,Ltd |
| 6/13/1995 | Allergen Extract | Novo-Helisen Depot initial treatment A | Allergic (IgE-mediated) disease, such as allergic rhinitis, allergic conjunctivitis, allergic bronchial asthma etc., triggered by the inhalation of unavoidable allergens. Specific immunotherapy is currently the only causal therapy available for treatment of IgE-mediated allergic diseases. | Allerpha International |
| 6/13/1995 | Allergen Extract | Novo-Helisen Depot initial treatment B | Allergic (IgE-mediated) disease, such as allergic rhinitis, allergic conjunctivitis, allergic bronchial asthma etc., triggered by the inhalation of unavoidable allergens. Specific immunotherapy is currently the only causal therapy available for treatment of IgE-mediated allergic diseases. | Allerpha International |
| 6/13/1995 | Allergen Extract | Novo-Helisen Depot initial treatment C | Allergic (IgE-mediated) disease, such as allergic rhinitis, allergic conjunctivitis, allergic bronchial asthma etc., triggered by the inhalation of unavoidable allergens. Specific immunotherapy is currently the only causal therapy available for treatment of IgE-mediated allergic diseases. | Allerpha International |
| 6/13/1995 | Allergen Extract | Novo-Helisen Depot initial treatment D | Allergic (IgE-mediated) disease, such as allergic rhinitis, allergic conjunctivitis, allergic bronchial asthma etc., triggered by the inhalation of unavoidable allergens. Specific immunotherapy is currently the only causal therapy available for treatment of IgE-mediated allergic diseases. | Allerpha International |

| Approval | Generic Name | Trade Name | Indication | Company |
|---|---|---|---|---|
| 6/14/1995 | Allergen Extract | Allergenic extracts for scratch test | Identification of causative allergenic disease such as allergic asthma and allergic rhinitis. | Allerpha International |
| 10/9/1995 | Activated factor 9 complex | Autoplex-T | Hemophiliac patient with inhibitor. | The Republic of Korea National Red Cross |
| 1/25/1996 | Anti D(Rho) immunoglobuline | Partobulin injection | Prevention D (Rho) sensitization in mother/recipient or fetus/child transfused blood, or when the rhesus factor of the fetus/child is unknown or cannot be determined. | Dalim Corp. |
| 11/2/1996 | Riluzole | Rilutek | Treatment of patients with amyotrophic lateral sclerosis. Rilutek extends survival time and/or time to tracheostomy. | Aventis Pharmaceutical Co., Ltd. |
| 1/23/1997 | Abciximab | ReoPro solution for injection | An adjunct to heparin and aspirin for the prevention of ischaemic cardiac complications in high risk patients undergoing percutaneous coronary intervention. | Lilly Korea Ltd. |
| 2/3/1997 | Cladribine | Leustatin injection | Treatment of active hairy cell leukemia. | Janssen Korea Ltd. |
| 4/8/1997 | 0.015 mg of plant extract from 0.02mg of mistletoe (host tree Abietis) | ABNOBAviscum A 0.02mg solution for injection | Treatment of tumors; prevention of recurrence following tumor surgery; treatment of malignant diseases of haematopoetic organs. | Korea Abnoba Co., Ltd. |
| 4/8/1997 | 0.15 mg of plant extract from 0.2mg of mistletoe (host tree Abietis) | ABNOBAviscum A 0.2mg solution for injection | Treatment of tumors; prevention of recurrence following tumor surgery; treatment of malignant diseases of haematopoetic organs. | Korea Abnoba Co., Ltd. |
| 4/8/1997 | 15 mg of plant extract from 20mg of mistletoe (host tree Abietis) | ABNOBAviscum A 20mg solution for injection | Treatment of tumors; prevention of recurrence following tumor surgery; treatment of malignant diseases of haematopoetic organs, pre-cancerous conditions; stimulation of bone marrow function. | Korea Abnoba Co., Ltd. |
| 4/8/1997 | 1.5 mg of plant extract from 2mg of mistletoe (host tree Abietis) | ABNOBAviscum A 2mg solution for injection | Treatment of tumors; prevention of recurrence following tumor surgery; treatment of malignant diseases of haematopoetic organs. | Korea Abnoba Co., Ltd. |
| 4/8/1997 | 0.015 mg of plant extract from 0.02mg of mistletoe (host tree Fraxini) | ABNOBAviscum F 0.02mg solution for injection | Treatment of tumors; prevention of recurrence following tumor surgery; treatment of malignant diseases of haematopoetic organs. | Korea Abnoba Co., Ltd. |

| Approval | Generic Name | Trade Name | Indication | Company |
|---|---|---|---|---|
| 4/8/1997 | 0.15 mg of plant extract from 0.2mg of mistletoe (host tree Fraxini) | ABNOBAviscum F 0.2mg solution for injection | Treatment of tumors; prevention of recurrence following tumor surgery; treatment of malignant diseases of haematopoetic organs. | Korea Abnoba Co., Ltd. |
| 4/8/1997 | 15 mg of plant extract from 20mg of mistletoe (host tree Fraxini) | ABNOBAviscum F 20mg solution for injection | Treatment of tumors; prevention of recurrence following tumor surgery; treatment of malignant diseases of haematopoetic organs, pre-cancerous conditions; stimulation of bone marrow function. | Korea Abnoba Co., Ltd. |
| 4/8/1997 | 1.5 mg of plant extract from 2mg of mistletoe (host tree Fraxini) | ABNOBAviscum F 2mg solution for injection | Treatment of tumors; prevention of recurrence following tumor surgery; treatment of malignant diseases of haematopoetic organs. | Korea Abnoba Co., Ltd. |
| 4/8/1997 | 0.015 mg of plant extract from 0.02mg of mistletoe (host tree Mali) | ABNOBAviscum M 0.02mg solution for injection | Treatment of tumors; prevention of recurrence following tumor surgery; treatment of malignant diseases of haematopoetic organs. | Korea Abnoba Co., Ltd. |
| 4/8/1997 | 0.15 mg of plant extract from 0.2mg of mistletoe (host tree Mali) | ABNOBAviscum M 0.2mg solution for injection | Treatment of tumors; prevention of recurrence following tumor surgery; treatment of malignant diseases of haematopoetic organs. | Korea Abnoba Co., Ltd. |
| 4/8/1997 | 15 mg of plant extract from 20mg of mistletoe (host tree Mali) | ABNOBAviscum M 20mg solution for injection | Treatment of tumors; prevention of recurrence following tumor surgery; treatment of malignant diseases of haematopoetic organs, pre-cancerous conditions; stimulation of bone marrow function. | Korea Abnoba Co., Ltd. |
| 4/8/1997 | 1.5 mg of plant extract from 2mg of mistletoe (host tree Mali) | ABNOBAviscum M 2mg solution for injection | Treatment of tumors; prevention of recurrence following tumor surgery; treatment of malignant diseases of haematopoetic organs. | Korea Abnoba Co., Ltd. |
| 4/8/1997 | 0.015 mg of plant extract from 0.02mg of mistletoe (host tree Quercus) | ABNOBAviscum Q 0.02mg solution for injection | Treatment of tumors; prevention of recurrence following tumor surgery; treatment of malignant diseases of haematopoetic organs. | Korea Abnoba Co., Ltd. |
| 4/8/1997 | 0.15 mg of plant extract from 0.2mg of mistletoe (host tree Quercus) | ABNOBAviscum Q 0.2mg solution for injection | Treatment of tumors; prevention of recurrence following tumor surgery; treatment of malignant diseases of haematopoetic organs. | Korea Abnoba Co., Ltd. |

| Approval | Generic Name | Trade Name | Indication | Company |
|---|---|---|---|---|
| 4/8/1997 | 15 mg of plant extract from 20mg of mistletoe (host tree Quercus) | ABNOBAviscum Q 20mg solution for injection | Treatment of tumors; prevention of recurrence following tumor surgery; treatment of malignant diseases of haematopoetic organs, pre-cancerous conditions; stimulation of bone marrow function. | Korea Abnoba Co., Ltd. |
| 4/8/1997 | 1.5 mg of plant extract from 2mg of mistletoe (host tree Quercus) | ABNOBAviscum Q 2mg solution for injection | Treatment of tumors; prevention of recurrence following tumor surgery; treatment of malignant diseases of haematopoetic organs. | Korea Abnoba Co., Ltd. |
| 4/17/1997 | Interferon beta-1b | Beneserin solution | Relapsing-remitting multiple sclerosis, secondary progressive multiple sclerosis. | Schering-Plough Korea Ltd. |
| 10/31/1997 | Ritonavir | Novir Soft gelatin capsule | HIV infection. | Abbott Korea, Ltd. |
| 10/31/1997 | Ritonavir | Novir solution | HIV infection. | Abbott Korea, Ltd. |
| 11/5/1997 | Sizofiran 10mg per 1ml | Sonifilan injection | Increase of direct effect of radiation therapy for cervical cancer. | Kwang Dong Pharmaceutical Co., Ltd. |
| 12/24/1997 | Allergenic extracts | Allergenic extracts for treatment | Treatment of allergenic diseases such as allergic asthma and allergic rhinitis (immunotherapy). | Dae-Yei C. |
| 12/24/1997 | Outermembrane protein of pseudomonas aerugimosa | Peudovaccin | Prevention of pseudomonas infection and sepsis in severely burned patients. | CJ Corp. |
| 12/24/1997 | Allergen extracts | Prescription treatment set | Treatment of allergenic diseases such as allergic asthma and allergic rhinitis. | Dae-Yei Co. |
| 1/15/1998 | Lanreotide | Somatuline LA | 1. Treatment of individuals with acromegaly when the secretion of growth hormone remains abnormal after surgery and/or radiotherapy. 2. Treatment of symptoms (flushes and diarrhea, etc.) associated with neuroendocrine tumors (Carcinoid tumors). | Beaufour Ipsen Korea |
| 2/9/1998 | Amsacrine | Amsidyl injection | Indication for induction of remission and maintenance in acute adult leukemia. It is said to be effective when using the combined therapy or singleness therapy against refractory to early stage in the induction therapy of anthracycline or other anti cancer drug. | Myung Ji Pharmaceutical Co., Ltd. |
| 2/18/1998 | Purified House Dust Mite allergen extract | Alutard-SQ house dust mites (initial course) | Specific immune therapy about IgE mediated allegoric diseases; treatment of rhinitis, conjunctivitis, asthma mediated Hose Dust Mites. | Green Cross Co. |

| Approval | Generic Name | Trade Name | Indication | Company |
|---|---|---|---|---|
| 2/18/1998 | Purified house dust mite allergen extract | Alutard-SQ house dust mites (maintenance course) | Specific immune therapy about IgE mediated allegoric diseases; treatment of rhinitis, conjunctivitis, asthma mediated Hose Dust Mites. | Green Cross Co. |
| 5/11/1998 | Polifeprosan 20 with carmustine implant | Gliadel Wafer | Use as an adjunct to surgery to prolong survival in patient with recurrent glioblastoma multiforme for whom surgical resection is indicated. | Aventis Pharmaceutical Co., Ltd. |
| 7/9/1998 | Fludarabine phosphate | Fludara injection | Treatment of patients with B-cell chronic lymphocytic leukemia (CLL) at Binet stage B have not responded to or whose disease has progressed during or after treatment with at least one standard alkylating-agent containing regimen. | Schering-Plough Korea Ltd. |
| 7/30/1998 | Daclizumab | Zenapax | Prophylaxis of acute organ rejection in patients receiving renal transplants. It is used concomitantly with an immunosuppressive regimen, including cyclosporine and corticosteroids. | Roche Korea Co., Ltd. |
| 8/13/1998 | Factor VIII Inhibitor Bypassing Activity Complex (200~600 mg as plasma protein) | Feiba TIM 4 injection | Therapy and prophylaxis of hemorrhage and to cover surgical intervention in Hemophilia A patients with FVIII inhibitor; Hemophilia B patients with FIX inhibitor. | The Republic of Korea National Red Cross |
| 8/17/1998 | Oprelvekin (recombinant) | Neumega | Prevention of severe thrombocytopenia and the reduction of the need for platelet transfusions following myelosuppressive chemotherapy in patients with nonmyeloid malignancies who are at high risk of severe thrombocytopenia. Neumega is not indicated following myeloablative chemotherapy. | Wyeth Korea, Inc. |
| 8/31/1998 | Pentosan polysulfate sodium | Elmiron (pentosan polysulfate sodium) capsule | Relief of bladder pain or discomfort associated with interstitial cystitis. | Cho-a Pharmaceutical Co., Ltd. |
| 10/2/1998 | Enocitabine 250mg | Sunrabin injection | Acute leukemia (including acute transforming of the chronic leukemia). | Chong Kun Dang Pharmaceutical Corp. |

| Approval | Generic Name | Trade Name | Indication | Company |
|---|---|---|---|---|
| 10/16/1998 | Eptacog alfa (activated) 60 KIU (1.2 mg) / 120 KIU (2.4 mg) / 240 KIU (4.8 mg) | NovoSeven injection 60 KIU / 120 KIU / 240 KIU | Serious bleeding events and surgery in patients with inhibitors to coagulation factors (FVIII or FIX). | Novo Nordisk Pharmaceutical Korea Ltd. |
| 11/4/1998 | Stavudine | Zerit capsule 15mg, 20mg, 30mg, 40mg | Treatment of HIV infected patients who have received prolonged prior zidovudine therapy. | BMS Korea Ltd. |
| 11/18/1998 | Cytomegalo virus immuneglobulin-G | Cytogam injection | Attenuation of primary cytomegalovirus disease associated with kidney transplantation. | Hyun Dae Pharmaceutical Co., Ltd. |
| 11/18/1998 | Human - cytomegalovirus-immunoglobulin | Megalotect injection | Prophylaxis of clinical manifestations of cytomegalovirus infection in patients subjected to immunosuppressive therapy, particularly in bone marrow or solid organ transplant recipients. | Korean Drug Co., Ltd. |
| 12/22/1998 | Rituximab | Mabthera | 1. Treatment of patients with relapsed or chemoresistant follicular lymphoma (Types B-D of IWF of B-cell non-Hodgkin's lymphoma); 2. Treatment of CD20 positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP chemotherapy (8 cycles of cyclophosphamide, doxorubicin, vincristine, prednisone). | Roche Korea Co., Ltd. |
| 12/30/1998 | Aldesleukin 18 million IU per vial | Proleukin | Treatment of metastatic renal cell carcinoma. Risk factors associated with decreased response rates and median survival are a performance status of ECOG 1 or greater; more than one organ with metastic disease sites a period of less than 24 months between initial diagnosis of primary tumor and the date the patient is evaluated for proleukin treatment; response rates and median survival decrease with the number of risk factors present. A patient positive for all three risk factors should not be treated with Proleukin. | Hyup Jin Corp. |
| 1/14/1999 | Nevirapine hemihydrate | Viramune suspension | A concomitant antiviral therapy for patients infected with HIV-2 with progressive deterioration of immune functions or before the onset of the disease. | Boehringer Ingelhein Korea Ltd. |

| Approval | Generic Name | Trade Name | Indication | Company |
|---|---|---|---|---|
| 2/1/1999 | Nelfinavir mesylate | Viracept tab powder | Treatment of HIV infection when antiretrovial therapy is warranted. | Dong-a Pharmaceutical Co., Ltd. |
| 2/1/1999 | Nevirapine anhydrate | Viramune tablets | A concomitant antiviral therapy for patients infected with HIV-1 with progressive deterioration of immune functions or before the onset of the disease. | Dong-a Pharmaceutical Co., Ltd. |
| 2/19/1999 | Basiliximab 20mg | Simulect injection | In adults: prophylaxis of acute organ rejection in renal transplantation using immunosuppressants like cyclosporin, corticosteroid, etc. or using triple therapy of cyclosporin, corticosteroid and azathioprine or mycophenolate mofetil. In children: prophylaxis of acute organ rejection in renal transplantation using immunosuppressants like cyclosporin, corticosteroid, etc. | Novartis Korea Ltd. |
| 2/27/1999 | Edetate calcium disodium | Bleian injection | Treatement of lead poisoning. | Dalim Corp. |
| 3/5/1999 | (6R,S)-5,6,7,8-tetrahydro-L-biopterin dihydrochloride | Tetrahydrobiopterin tablet | Atypical phenylketonuria. | Stiefel Laboratories Korea, Ltd. |
| 3/13/1999 | Efavirenz | Stocrin | Treatment of HIV-1infection in combination with other antiretroviral agents. This indication is based on analysis of plasma HIV-RNA levels and CD4 cell counts in controlled studies of up to 24 weeks in duration. At present, there are no results from controlled trials evaluation long-term suppression of HIV-RNA with Stocrin. | MSD Korea Ltd. |
| 6/18/1999 | Corticorelin trifluoroacetate | CRH Ferring | Diagnosis of pituitary fuction. | Ferring Pharmceutical Korea Ltd. |
| 6/18/1999 | Somatorelin acetate | GHRH Ferring | Diagnosis of pituitary fuction. | Ferring Pharmaceuticals Korea Ltd. |
| 7/16/1999 | Saquinavir | Fortovase | Treatment of advanced immunodificient patients with HIV infection in combination with other antiretroviral agents. | Roche Korea Co., Ltd. |
| 7/20/1999 | Becaplermin | Regranex gel 0.01% | Treatment of acute allograft rejection in renal transplant patients. | Janssen Korea Ltd. |
| 8/10/1999 | Lepirudin | Refludan | Treatment for heparin-induced thrombocytopenia type ll. | Handok Pharmaceutical Co., Ltd. |

| Approval | Generic Name | Trade Name | Indication | Company |
|---|---|---|---|---|
| 9/18/1999 | Octreotide 10mg, 20mg | Sandostatin Lar injection | 1. Treatment of acromegaly in patients who are adequately controlled on s.c. treatment with Sandostatin. Patients in whom surgery, radiotherapy or dopamine agonist treatment is inappropriate or ineffective, or in the interim period until radiotherapy becomes fully effective. 2. Alleviation of symptoms associated with gastro-entero-pancreatic endocrine tumor carcinoid tumors with features of carcinoid syndrome. | Novartis Korea Ltd. |
| 10/18/1999 | Anagrelide hydrochloride | Agrylin capsule | Treatment of patients with thrombocythemia, secondary to myeloproliferative disorders (Essential thrombocythaemia, Chronic myelogenous leukemia, Polycythaemia and other myeloproliferative disorders), to reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms including thrombo-hemorrhagic events. | Yuhan Corp. |
| 2/22/2000 | Trastuzumab | Herceptin | Treatment of patients with metastatic breast cancer who have tumors that overexpress HER2:1; as monotherapy for the treatment of patients who have received one or more chemotherapy regimens for their metastatic disease; in combination with paclitaxel for the treatment of patients who have not received chemotherapy for their metastatic disease. | Roche Korea Co., Ltd. |
| 3/5/2000 | Dantrolene sodium | Dantrolene | Treatment of malignant hyperthermia crisis syndrome. | Korea Orphan Drug Center |
| 3/29/2000 | Tirofiban hydrochloride | Agrastat | Treatment of acute coronary syndrome including patients who are to be managed medically and those undergoing percutaneous transluminal coronary angioplasty (PTCA) or atherectomy. In this setting, Agrastat has been shown to decrease the rate of a combined endpoint of death, new myocardial infarction or refractory ischemia/repeat cardiac procedure. | MSD Korea Ltd. |

| Approval | Generic Name | Trade Name | Indication | Company |
|---|---|---|---|---|
| 4/12/2000 | Recombinant Human Interferon beta-1a 22mg or 44mg | Rebif | Treatment of ambulatory patients with relapsing-remitting multiple sclerosis chrarcterized by at least 2 recurrent attacks of neurological dysfunction over the preceding 2-year period. | Serono Korea Co., Ltd. |
| 5/23/2000 | Exemestane | Aromasin tab 25mg | Treatment of advanced breast cancer in women with natural or induced postmenopausal status whose disease has progressed following anti-oestrogen therapy and either non-steroidal aromatase inhibitors or progestins for the third-line hormonal treatment. | Pharmacia & Upjohn Ltd. |
| 8/29/2000 | Desmopressin acetate | Octostim Nasal Spray | Control of bleeding and bleeding prophylaxis in patients with mild haemophilia A and von Willebrand's disease. | Ferring Pharmaceutical Korea Ltd. |
| 10/19/2000 | Quinupristin and dalfopristin | Synercid injection | Treatment of the following infections when caused by susceptible strains of microorganisms: vancomycin-resistant Enterococcus faecium (VREF) bactermia. | Aventis Pharmaceutical Co., Ltd. |
| 10/21/2000 | Infliximab | Remicade | Reducing signs and symptoms and inducing and maintaining clinical remission in patients with moderately to severely active Crohn’s disease who have had an inadequate response to conventional therapy. Remicade is also indicated for the reduction in the number of draining enterocutaneous fistulae in patients with fistulizing Crohn's disease. | Schering-Plough Korea Ltd. |
| 12/11/2000 | Temozolomide | Temodar | Treatment of patients with refractory anaplastic astrocytoma and refractory glioblastoma multiforme, i.e., patients at first relapse who have experienced disease progression on a standard regimen. | Schering-Plough Korea Ltd. |
| 1/3/2001 | Cetrorelix Acetate 0.265mg | Cetrotide | The inhibition of premature LH surges in women undergoing controlled ovarian stimulation in IVF. | Serono Korea Co., Ltd. |
| 1/22/2001 | IgM enriched Human immunoglobulin | Pentaglobin injection | Adjuvant therapy of severe bacterial infections additional to antibiotic therapy; immunoglobulin substitution in immunocompromised patients. | Korean Drug Co., Ltd. |
| 2/16/2001 | Hematoporphyrin derivatives | Photogem injection | Treatment of obstructing esophageal cancer, obstructing lung cancer skin basal cell cancer, obstructing pharingeal cancer, in which radiation of laser light can be applied to and can be examined endoscopically. | PDT Korea Corp. |
| 2/19/2001 | Hemin | Panhematin | Porphyria. | Abbott Korea, Ltd. |

| Approval | Generic Name | Trade Name | Indication | Company |
|---|---|---|---|---|
| 4/2/2001 | Sodium nitrite, sodium thiosulfate, amyl nitrite | Cyanide antidote package | Treatment of cyanide poisoning. | Haeng Lim Pharmaceutical Co., Ltd. |
| 5/7/2001 | 5-Hydroxytryptophan | 5- HTP capsule | Phenylketonuria | Korea Orphan Drug Center |
| 5/30/2001 | Recombinant human Epidermal Growth Factor (rhEGF) | Easyef dermal solution 0.005% | Diabetic foot ulcers. | Daewoong Pharmaceutical Co., Ltd. |
| 6/14/2001 | Abacavir | Ziagen | Treatment of HIV-1 infection in combination with other antiretroviral agents. | GlaxoSmithKline Korea Ltd. |
| 6/15/2001 | Indomethacin sodium | Indocin | Prophylaxis and treatment of patent ductus arteriosus in infants. | MSD Korea Ltd. |
| 6/20/2001 | Imatinib mesylate 100mg | Glivec capsule | 1) Philadelphia chromosome positive chronic myeloid leukemia in blast crisis, accelerated phase and chronic phase; 2) c-kit positive unresectable or malignant gastrointestinal stromal tumors. | Novartis Korea Ltd. |
| 1/14/2002 | Thyrotropin (TSH) alfa | Thyrogen injection | Thyroid globulin test or whole body scanning for recurrence possibility and/or metastasis of thyroid cancer, it is administered to maintain proper plasma concentration of thyroid stimulating hormone. | Sam-Oh Pharmaceutical Co., Ltd. |
| 3/6/2002 | Glatiramer acetate | Copaxone | Treatment of relapsing-remitting multiple sclerosis. | Aventis Pharmaceutical Co., Ltd. |
| 3/13/2002 | Rho(D) Immune globulin (human) for injection | WinRho SDF | Treatment of immune thrombocytopenic purpura (ITP). | Jung In Pharmaceutical Trading Co. |
| 3/20/2002 | Immunocyanine | Immucothel | Prevention of bladder carcinoma recurrences after surgical removal of a bladder carcinoma and in cases where other established therapies have failed. | Ahn-Gook Pharm.Co., Ltd. |
| 4/29/2002 | Rasburicase 1.50mg | Fasturtec injection | Hyperuricemia in chemotherapy patients for malignant tumors. | Sanofi-Synthelabo Korea Ltd. |
| 6/3/2002 | Allergen Extract | Tyrosine S continuation course A | Treatment of allergic diseases e.g. hayfever (allergic rhinitis), allergic conjunctivitis or allergic bronchial asthma due to an IgE-mediated allergy. | Shin Kwang New Drugs Co., Ltd. |
| 6/3/2002 | Allergen Extract | Tyrosine S continuation course B | Treatment of allergic diseases e.g. hayfever (allergic rhinitis), allergic conjunctivitis or allergic bronchial asthma due to an IgE-mediated allergy. | Shin Kwang New Drugs Co., Ltd. |

| Approval | Generic Name | Trade Name | Indication | Company |
|---|---|---|---|---|
| 6/3/2002 | Allergen Extract | Tyrosine S continuation course C | Treatment of allergic diseases e.g. hayfever (allergic rhinitis), allergic conjunctivitis or allergic bronchial asthma due to an IgE-mediated allergy. | Shin Kwang New Drugs Co., Ltd. |
| 6/3/2002 | Allergen Extract | Tyrosine S continuation course D | Treatment of allergic diseases e.g. hayfever (allergic rhinitis), allergic conjunctivitis or allergic bronchial asthma due to an IgE-mediated allergy. | Shin Kwang New Drugs Co., Ltd. |
| 6/3/2002 | Allergen Extract | Tyrosine S continuation course H | Treatment of allergic diseases e.g. hayfever (allergic rhinitis), allergic conjunctivitis or allergic bronchial asthma due to an IgE-mediated allergy. | Shin Kwang New Drugs Co., Ltd. |
| 6/3/2002 | Allergen Extract | Tyrosine S continuation course I | Treatment of allergic diseases e.g. hayfever (allergic rhinitis), allergic conjunctivitis or allergic bronchial asthma due to an IgE-mediated allergy. | Shin Kwang New Drugs Co., Ltd. |
| 6/3/2002 | Allergen Extract | Tyrosine S continuation course J | Treatment of allergic diseases e.g. hayfever (allergic rhinitis), allergic conjunctivitis or allergic bronchial asthma due to an IgE-mediated allergy. | Shin Kwang New Drugs Co., Ltd. |
| 6/3/2002 | Allergen Extract | Tyrosine S treatment course A | Treatment of allergic diseases e.g. hayfever (allergic rhinitis), allergic conjunctivitis or allergic bronchial asthma due to an IgE-mediated allergy. | Shin Kwang New Drugs Co., Ltd. |
| 6/3/2002 | Allergen Extract | Tyrosine S treatment course B | Treatment of allergic diseases e.g. hayfever (allergic rhinitis), allergic conjunctivitis or allergic bronchial asthma due to an IgE-mediated allergy. | Shin Kwang New Drugs Co., Ltd. |
| 6/3/2002 | Allergen Extract | Tyrosine S treatment course C | Treatment of allergic diseases e.g. hayfever (allergic rhinitis), allergic conjunctivitis or allergic bronchial asthma due to an IgE-mediated allergy. | Shin Kwang New Drugs Co., Ltd. |
| 6/3/2002 | Allergen Extract | Tyrosine S treatment course D | Treatment of allergic diseases e.g. hayfever (allergic rhinitis), allergic conjunctivitis or allergic bronchial asthma due to an IgE-mediated allergy. | Shin Kwang New Drugs Co., Ltd. |
| 6/3/2002 | Allergen Extract | Tyrosine S treatment course E | Treatment of allergic diseases e.g. hayfever (allergic rhinitis), allergic conjunctivitis or allergic bronchial asthma due to an IgE-mediated allergy. | Shin Kwang New Drugs Co., Ltd. |
| 6/3/2002 | Allergen Extract | Tyrosine S treatment course F | Treatment of allergic diseases e.g. hayfever (allergic rhinitis), allergic conjunctivitis or allergic bronchial asthma due to an IgE-mediated allergy. | Shin Kwang New Drugs Co., Ltd. |

| Approval | Generic Name | Trade Name | Indication | Company |
|---|---|---|---|---|
| 6/3/2002 | Allergen Extract | Tyrosine S treatment course G | Treatment of allergic diseases e.g. hayfever (allergic rhinitis), allergic conjunctivitis or allergic bronchial asthma due to an IgE-mediated allergy. | Shin Kwang New Drugs Co., Ltd. |
| 6/3/2002 | Allergen Extract | Tyrosine S treatment course H | Treatment of allergic diseases e.g. hayfever (allergic rhinitis), allergic conjunctivitis or allergic bronchial asthma due to an IgE-mediated allergy. | Shin Kwang New Drugs Co., Ltd. |
| 6/3/2002 | Allergen Extract | Tyrosine S treatment course I | Treatment of allergic diseases e.g. hayfever (allergic rhinitis), allergic conjunctivitis or allergic bronchial asthma due to an IgE-mediated allergy. | Shin Kwang New Drugs Co., Ltd. |
| 6/3/2002 | Allergen Extract | Tyrosine S treatment course J | Treatment of allergic diseases e.g. hayfever (allergic rhinitis), allergic conjunctivitis or allergic bronchial asthma due to an IgE-mediated allergy. | Shin Kwang New Drugs Co., Ltd. |
| 8/8/2002 | Lanreotide | Somatuline | N/A | Beaufour Ipsen Pharma |
| 8/16/2002 | Coagulation Factor IX (recombinant) | Benefix | For the control and prevention of hemorrhagic episodes in patients with hemophilia B (congenital factor IX deficiency or Christmas disease), including control and prevention of bleeding in surgical settings. | Schering-Plough Korea Ltd. |
| 9/10/2002 | Lopinavir/Ritonavir | Kaletra capsule | HIV infection. | Abbott Korea, Ltd. |
| 9/10/2002 | Lopinavir/Ritonavir | Kaletra solution | HIV infection. | Abbott Korea, Ltd. |
| 9/17/2002 | Disodium clodronate | Bonefos capsule | Treatment of hypercalcemia and osteolysis due to malignancy. | Schering-Plough Korea Ltd. |
| 9/17/2002 | Disodium clodronate | Bonefos solution | Treatment of hypercalcemia and osteolysis due to malignancy. | Schering-Plough Korea Ltd. |
| 9/25/2002 | Agalsidase beta | Fabrazyme injection | Long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease. | Sam-Oh Pharmaceutical Co., Ltd. |
| 10/7/2002 | Ganciclovir | Cymevene | Prevention and treatment of CMV disease in SOT and immunocompromised patients including AIDS. | Roche Korea Co., Ltd. |
| 4/17/2004 | Valganciclovir | Valcyte | N/A | Pantheon Inc. |
| 7/29/2004 | Laronidase | Aldurazyme | N/A | Genzyme USA |
| 8/17/2004 | Atazanavir sulfate | Reyataz | N/A | Bristol-Myers Squibb USA |
| 9/10/2004 | Gemtuzumab ozogamicin | Mylotarg | N/A | Wyeth-Ayerst Lederle, Inc. |
| 10/4/2004 | Palivizumab | Synagis | N/A | Abbott Laboratories Ltd. / Boehringer Ingelheim Pharma KG |

| Approval | Generic Name | Trade Name | Indication | Company |
|---|---|---|---|---|
| 10/7/2004 | Efalizumab | Raptiva | N/A | Genentech, Inc. |
| 12/20/2004 | Iloprost | Ventivis | N/A | Berlimed SA |
| 12/30/2004 | Human Plasma-Derived Coagulation Factor VIII Concentrate | Immunate | N/A | Baxter |
| 5/16/2005 | Polifeprosan 20 with carmustine implant | Gliadel Wafer | N/A | Guilford Pharmaceuticals Inc. |
| 6/15/2005 | Lepirudin | Refludan | N/A | Pharmion Ltd. |
| 6/20/2005 | Sodium phenylbutyrate | Buphenyl | N/A | Ucyclyd Pharma Inc. |
| 8/12/2005 | Diazoxide | Proglycem | N/A | IVAX Research Inc. |
| 11/15/2005 | Alemtuzumab | Mabcampath | N/A | Bayer Schering Pharma |
| 11/28/2005 | Allergen extract | TRUE Test | N/A | Mekos Laboratories AS |
| 12/26/2007 | Nilotinib | Tasigna | N/A | Novartis Korea |
| 12/27/2007 | Decitabine | Dacogen | N/A | Janssen Korea Ltd. |
| 7/9/2008 | Trientine | Syprine | N/A | Merck & Co., Inc. |

# 8. HONG KONG

## 8.1 OVERVIEW

Hong Kong boasts a small yet wealthy population and the country's healthcare standards are among the highest in Asia. The pharmaceutical market is valued at around $7 billion and offers advanced technology and a very high standard of care. While there are a number of Hong Kong-based drug manufacturers, more advanced drugs are generally imported.

## 8.2 HONG KONG HEALTH AUTHORITY

The Department of Health (DOH) is responsible for health legislation and policy in Hong Kong. The DOH is made up of a number of smaller divisions, including the Medical Device Control Office, Center for Health Protection, Dental Service, Radiation Health and Drug Office. The Drug Office sector is responsible for drug registration and drug import/export control in Hong Kong.

## 8.3 ORPHAN DRUGS IN HONG KONG

### 8.3.1 Orphan Drug Application Process

According to the *Guidance Notes on Registration of Pharmaceutical Products* (September 2005), all drugs must be registered with the Pharmacy and Poisons Board in Hong Kong before they can be offered for sale, distributed or sold. The applicant should be located in Hong Kong, i.e., an importer, distributor, or representative of a Hong Kong branch, subsidiary of the manufacturer or other type of local office. Separate applications should be submitted for variations in dosage form and strength; however, different package sizes do not require separate applications.

An orphan drug applicant may register their drug under the New Chemical Entity (NCE) registration process, which was established for new, life-saving drugs. In this case, the application will be processed immediately and reviewed by the Hong Kong Department of Health (DOH) Pharmaceutical Licensing Committee. This Committee only meets four times a year, so applicants should make an effort to submit their application several weeks prior to a Committee meeting in order to reduce processing time.

A second registration process is available for those applicants who cannot meet the NCE application requirements. The second option, registering under the "normal" registration process, takes 6-9 months to complete. Application forms should be turned into the Drug Registration and Import/Export Division. The application fee is $1,100 Hong Kong Dollars (about $142 US Dollars). For detailed information for application requirements, refer to the guidelines posted on the Drug Office of the Department of Health website (http://www.drugoffice.gov.hk/eps/do/en/doc/guidelines_forms/guid.pdf)

A third option is also available, wherein the applicant can avoid the drug registration process altogether and get their drug into the Hong Kong market via a Named Patients Program. In this case, a distributor can apply for importation of the orphan drug on behalf of supporting doctors in Hong Kong. The doctors will need to provide a letter to the DOH indicating the amount of the orphan drug required to treat their patients.

Note: Orphan drug companies should keep in mind that it is possible to proceed with the NCE registration process while simultaneously entering into the Named Patients Program. Regarding sales, companies should keep in mind that in Hong Kong, pharmaceutical products, including orphan drugs, are not reimbursable unless a product is specifically listed on the hospital list of supplies. The best way to get an orphan drug on the hospital list of supplies is via very strong doctor support and active lobbying by the patients/parents. In addition, once an importer is importing an orphan drug, they will be the only importer that can sell the drug in Hong Kong.

While a list of orphan drug approvals in Hong Kong is not available, a comprehensive and searchable database of *all* drug approvals in Hong Kong can be found at http://www.drugoffice.gov.hk/eps/do/en/consumer/search_drug_database.html.

### 8.3.2 Hong Kong Orphan Drug Application Requirements

| | Required Documents and Information | Details |
|---|---|---|
| **1** | Free Sales Certificate from at least three countries including the country of origin | A Free Sale Certificate from the EU is considered to represent 27 countries |
| **2** | Evidence that the product is manufactured by a licensed manufacturer (e.g. certified true copy of manufacturer's license) | |
| **3** | Original registration certificate of existing product (if applicable) | |
| **4** | Application form | |
| **5** | Information on both active and inactive ingredients of product (e.g. complete master formula) | |
| **6** | Specifications of product | Physical description, uniformity of weight, disintegration time, identification, assay of active ingredients, etc. |
| **7** | Clinical papers in support of any new indications and claims that are not well documented in pharmacopoeias and for unusual combination of drug ingredients | |
| **8** | Method of analysis | |
| **9** | Three expert reports: Pharmaceutical Report, Clinical Report and Pharmacological Report | |
| **10** | One set of original (prototype) sales pack (outer carton) and container label of each pack size of product | If product is an over-the-counter medicine, sales pack label must include dosage, route, and frequency of use in both English and Chinese |
| **11** | Stability test data to justify proposed shelf life | Real-time and accelerated conditions |
| **12** | Certificate of analysis of representative batch of product | |
| **13** | Reference standard with enough samples for ten tests, including sterility testing | |

## Drug Registration Application Form (Form 6)

**APPLICATION FOR REGISTRATION OF A DRUG / PHARMACEUTICAL PRODUCT / SUBSTANCE**
**藥品 / 藥劑製品 / 物質註冊申請書**

*Note :* A specimen sales pack of the drug/product or sample of the substance and the relevant literature must be submitted together with the application. Supplementary documentation and supporting documents issued by the health authority in the Country of origin should be submitted if required.
註 : 藥品 / 藥劑製品的銷售樣品或物質的樣品以及有關的說明書須連同申請表一併呈交。如有需要，原產國家的衛生主管當局發出的補充文件及作支持用的文件亦須呈交。

Name of the Drug/Product/Substance* :
(*Delete as appropriate)
藥品 / 製品 / 物質* 的名稱
(*刪去不適用者)

Dose Form/Package Size(s) :
劑型 / 包裝大小 :

Detailed Qualitative and Quantitative Composition :
詳細的素質及分量成分組合 :

Indications :
用途 :

Names of Countries in which registered/marketed :
在何國家註冊 / 在何國家市場出售 :

Name of Applicant :
申請人姓名或名稱 :

Business Address of Applicant :
申請人營業地址

Tel. No. :
電話號碼 :

Name of Manufacturer :
製造商姓名或名稱 :

**DECLARATION OF APPLICANT**
**申請人聲明**

I hereby declare that to the best of my knowledge and belief the information given in this application is correct.
本人現聲明盡本人所知及所信，本申請書所報資料均屬正確。

Date : .....
日期 :

Signature : .....
簽署 :

**For Office Use Only**
**只供本辦事處填寫**

| Date Received 收件日期 | Forensic Classification 法醫學分類 | Fees Paid 已繳費用 | Registration Approved 獲准註冊 | Certificate Issued 已發的證明書 | Registration 註冊 |
|---|---|---|---|---|---|
| | | | | | |

## Drug Registration Application Checklist (Appendix 1)

**DEPARTMENT OF HEALTH** Appendix 1
**DRUG OFFICE**
**DRUG REGISTRATION AND IMPORT/EXPORT CONTROL DIVISION**

**CHECKLIST**

Application for Product/Substance Registration
Please lodge this checklist and arrange the documents in the following order with your application form.

| | | Yes | No |
|---|---|---|---|
| 1. | Is this a priority application?<br>(i). change of name, dosage form or active ingredient, please provide the original registration certificate of the existing product; or<br>(ii). change of product certificate holder, please provide a statement from manufacturer for the change. | ☐ | ☐ |
| 2. | Copy of business registration certificate of applicant? | ☐ | ☐ |
| 3. | Have you provided a covering letter from the applicant? | ☐ | ☐ |
| 4. | Have you provided an authorization letter from the manufacturer for products manufactured outside Hong Kong? | ☐ | ☐ |
| 5. | Have you provided evidence that the product is manufactured by a licensed manufacturer? (e.g. certified true copy of manufacturer's licence) | ☐ | ☐ |
| 6. | Have you provide evidence of Good Manufacturing Practices (GMP) compliance of the manufacturer? (e.g. certified true copy of GMP Certificate of the manufacturer) | ☐ | ☐ |
| 7. | Have you provided evidence that the product is allowed for sale in the country of origin? (i.e. original or certified true copy of free sale certificate) | ☐ | ☐ |
| 8. | Is the product a new chemical or biological entity? | ☐ | ☐ |
| 9. | Have you provided clinical and scientific papers as required? | ☐ | ☐ |
| 10. | Have you enclosed one set of prototype sales pack (outer carton) and container label of each pack size of your product?<br>If product under application is an over-the-counter product, the dosage, route and frequency of administration are required to be labeled in both English and Chinese. | ☐ | ☐ |
| 11. | Have you enclosed copy of documents to support the proposed indication(s), dosage, route of administration and other contents of the package insert (if any) ? | ☐ | ☐ |
| 12. | (i) Have you provided the scanned image (not less than 300dpi) or photograph of pixel size (not less than 320x200) of your product sample, including sales pack, inner container/packaging and image of the drug sample or<br>(ii) sample of your substance as it will be sold to the purchaser? | ☐ | ☐ |
| 13. | Have you provided information on both active and inactive ingredients of your product? (i.e. complete master formula) | ☐ | ☐ |
| 14. | Have you provided the specifications issued by the manufacturer? Documents showing compliance with one or more of the following pharmacopoeias are required unless otherwise justified: Pharmacopoeia of the People's Republic of China, British Pharmacopoeia, European Pharmacopoeia, International Pharmacopoeia, Japanese Pharmacopoeia and/or United States Pharmacopoeia. | ☐ | ☐ |
| 15. | Have you provided the method of analysis of the product? | ☐ | ☐ |
| 16. | Have you provided a certificate of analysis of a representative batch of the product? | ☐ | ☐ |
| 17. | Have you provided stability test data to justify the proposed shelf-life? | ☐ | ☐ |
| 18. | Have you provided Bioequivalence data for anti-epileptic drugs? | ☐ | ☐ |

## 8.4 HEALTH AUTHORITY CONTACT INFORMATION

Department of Health
Address: 21/F, Wu Chung House, 213 Queen's Road East, Hong Kong
Phone: +85-2-2961-8989; +85-2-2961-8991
Fax: +85-2-2836-0071
Email: enquiries@dh.gov.hk
Website: http://www.dh.gov.hk

Drug Office, Department of Health
Address: 3/F Public Health Laboratory Centre, 382 Nam Cheong Street, Kowloon, Hong Kong
Phone: +85-2-2319-8458
Fax: +85-2-2803-4962
Email: pharmgeneral@dh.gov.hk
Website: http://www.drugoffice.gov.hk/eps/do/index.html

# 9. CHINA

## 9.1 OVERVIEW

China is the world's second largest economy after the US. With more than 1.3 billion people in China, the economic potential for foreign companies entering its market is enormous. Foreign companies have centered their business expansion on large urban areas, such as Beijing, Shanghai and Guangzhou. In addition to huge principal areas, many "second-tier" cities, such as Wuhan and Dalian, are also quickly catching up in prosperity and becoming excellent markets. However, China's rural interior still lags far behind these urban areas.

One significant growth area in China's economy is in its healthcare sector. As the country's citizens have begun to lead more affluent lifestyles due to the economic boom, their healthcare standards have increased. Many Chinese citizens are demanding better healthcare options and treatment. Additionally, pharmaceuticals are playing a much larger role in the Chinese lifestyle, especially in urban areas. However, the increased affluence and foreign influence on China has also led to changes in the country's epidemiological profile. Many Chinese are eating more and exercising less often. Now, chronic diseases, such as cardiovascular disease and cancer, are some of the leading causes of death.

## 9.2 PHARMACEUTICAL MARKET

China's pharmaceutical market is valued at about $65 billion and is expected to continue to experience enormous growth. China should rise to become the world's second largest drug market by 2016, and is expected to grow to more than $300 billion by 2020. The market is experiencing growth in both the over-the-counter (OTC) and prescription sectors, and is benefiting greatly from the influx of foreign drug companies expanding their manufacturing and R&D into China.

Foreign drug companies are significant players in China's drug market, though there are thousands of domestic pharmaceutical companies throughout the country. The majority of these domestic pharmaceuticals companies produce generic drugs and they neither have the technology nor meet the quality requirements to compete with the foreign companies. Some of these domestic companies have paired up with foreign companies in Sino-foreign joint ventures to be more competitive in the growing pharmaceutical market.

## 9.3 CHINA HEALTH AUTHORITY

The China Food and Drug Administration (CFDA) is responsible for regulating drugs in China, as well as medical devices, food and cosmetics. Pharmaceuticals are regulated under the *Drug Administration Law* (2001) and the *Regulation for the Implementation of the Drug Administration Law* (2002).

## 9.4 DRUG REGISTRATION PROCESS

### 9.4.1 Overview

Drug registration in China is a difficult process. For new drugs, it generally takes two years to complete. Moreover, the CFDA usually requires that a foreign company conduct clinical trials in China, even if the product has already been approved in another country. In China, drugs are classified into three types: chemical drugs, biological drugs and Traditional Chinese Medicines (TCMs).

Generally, pharmaceutical companies should not have trouble meeting the drug registration requirements for China, as these tend to be similar to those for other countries; the majority of the registration documents follow ICH guidelines. If problems do arise, they are usually related to the submission of sensitive and/or confidential information, such as the manufacturing process – information that foreign companies do not want to divulge. Prior to registration, drug companies should discuss their case with the Center for Drug Evaluation to determine the minimum registration requirements for their specific product.

The drug registration application fee is 45,300 Chinese Yuan (about $7,295; exchange rate 6.21). There is currently no separate application process for orphan drugs; they follow the normal drug registration standards.

### 9.4.2 China's New Drug Registration Requirements

| | Required Documents and Information | Details |
|---|---|---|
| **1** | Name of drug, chemical structure and formula | Include International Nonproprietary Name, chemical name, English name, and Chinese phonetics |
| **2** | Copy of manufacturing license and GMP certificate | |
| **3** | Drug discovery and development history, current production and marketing status | Synthesis process, selection of dosage form, determination of structure, etc. |
| **4** | Product insert, drafting notes, packaging and labeling | |
| **5** | Safety, efficacy, and quality control analysis | |
| **6** | Manufacturing process | |
| **7** | Quality validation | |
| **8** | Product specifications | |
| **9** | Sample testing report | |
| **10** | Active and inactive raw material specifications and testing report | |
| **11** | Stability information | |
| **12** | Pharmacology and toxicology reports | General pharmacology data; acute, single-dose, and long-term toxicology data |
| **13** | Pharmacodynamics report | |
| **14** | Research data on irritability**,** hemolysis, and local irritation | |
| **15** | Interaction data for pharmacodynamics, toxicology and pharmacokinetics of combination drug | |
| **16** | Mutagenicity data | |
| **17** | Reproductive toxicity data | |
| **18** | Carcinogenicity data | |
| **19** | Dependence data | |
| **20** | Pre-clinical pharmacokinetics data | |
| **21** | Summary of clinical research in China and in other foreign countries | Latest update on the clinical trials for the drug |
| **22** | Clinical study protocol and investigator's brochure | |
| **23** | Informed consent form, IRB approval document | |
| **24** | Clinical research report | |
| **25** | Specifications of immediate packaging material / container | |
| **26** | All information printed neatly and clearly | On A4-sized paper |

### 9.4.3 Application Process and Average Timeframe of Imported Drugs

1. Submit application
2. Dossier content and format checking, notification of quality test and specifications verification by CFDA (30 days)
3. Preliminary review by CFDA (5 days)
3. Technical evaluation by the CDE (120 days regular/100 days priority review)
4. *If necessary, CFDA requests supplementary data from applicant (response must be given within 4 months)*
5. *Supplementary data evaluation by the CDE (40 days regular/25 days priority review)*
6. Final review by CFDA (40 days regular/20 days priority review)
7. Approval for clinical trials
8. Notification of clinical trial protocol and list of investigators to CFDA
9. Commencement of Clinical Trials
10. Submission of clinical trial results and other amended or supplementary data
11. Acceptance by CFDA
12. Preliminary review by CFDA (5 days)
13. Technical evaluation by CDE (120 days regular/100 days priority review)
14. *If necessary, CFDA requests supplementary data from applicant (response must be given within 4 months)*
15. Final review by CFDA (40 days regular/20 days priority review)
16. Approval of drug marketing

**Imported Drug Registration Application Form**

Application Overview

1. Application Category： ○ Drugs imported for the first time

○ Previously foreign-approved

○ Uncertain of foreign approval status

○ Drugs imported more than once

2. Document classification: ○ Once-valid document ○ Multi-valid document

Drug Information

3. Chinese name:

4. Scientific name:

5. English name:

6. Other name(s):

7. Manufacturing country:

8. Exported country:

9. Amount included in application (in kilograms):

10. Packaging materials:

11. Packaging specifications:

12. Contract number:

13. Inspection standard：○ Chinese Pharmacopeia _____ Edition
○ Foreign Drug Standard, Source:_____
○ Herbal Drug Standard, Source:_____
○ Municipal/District Drug Standard, Source:_____
○ Independent Drug Approval Standard
(limited to drugs with an uncertain approval status)

14. Import Destination:

15. Import Destination's Food and Drug Administration Division:

16. Does it contain any endangered products? ○ Yes ○ No

17. Is this the first import for the manufacturing company?

○ Yes

○ No, number of imports: Amount imported (in kilograms):
Serial number:

18. Reason for application

Applicant

19. Company/agency (the agency is responsible for the application fee)
Company name:
Agency Number/Code:
Related Documents： 1. Business license number (《营业执照》):
2.○ Drug Manufacturing license number:
(《药品生产许可证》):
○GMP Certificate number (《药品经营许可证》):
Representative: Position title:
Representative's Address: Postal code:
Manufacture's address: Postal code:
Applicant name: Signature: Position title:
Phone number: Fax number:
Email address:
Contact: Phone number

Other information

20.Company/Agency (Exporting company)
Company name:
Agency number/code:
Business license number (《营业执照》):
Representative: Position title:
Address: Postal code:
Manufacturing address: Postal code:
Contact name: Phone number:

21.Company/Agency (Processing company)
Company name:
Agency number/code:
Business license number (《营业执照》):
Representative: Position title:
Address: Postal code:
Manufacturing address: Postal code:
Contact name: Phone number:

Statement

22. We guarantee that:

①The application has fulfilled the rules and regulations set forth by the 《中华人民共和国药品管理法》、《中华人民共和国药品管理法实施条例》and《进口药材管理办法》

②The application contains true information (ingredients, samples, development, statistics, clinical trials etc.)

③The online application matches the paper application.

If there are inconsistencies, we accept any responsibilities in these legal violations.

23. Other information:

24. Applicant Company stamp: Government representative stamp:

Date:

## 9.5 DRUG PRICING

Drug prices are regulated by the National Development and Reform Commission (NDRC) and the local provincial price bureau. After product registration, a pharmaceutical company should apply to the local provincial Price Bureau for pricing approval before the product is sold on the Chinese market. Documents regarding cost insurance, freight (CIF) price and cost analysis are required as part of the submission. Usually the price bureau will review the dossier and issue the price approval notification within 30 working days.

For drugs which are already included on the National Reimbursement Drug List, the NDRC has tight control over the highest permitted retail price. Companies which are original developers or patent holders can apply to the NDRC for *separate* pricing for their drugs included on the National Medical Insurance Drug List. However, even in such situations, the retail price granted will not be much higher than the maximum limit.

For drugs which are not on the list, pharmaceutical companies can suggest a retail price themselves. However, when the local government reviews price applications, they usually compare drugs in the same therapeutic area when determining pricing. A significant development in December 2010 was a ceiling imposed by the NDRC on retail prices of selected drugs in China. These drugs previously had prices fixed independently by the manufacturers. Most of these manufacturers were foreign-invested enterprises and joint ventures. More than 100 kinds of drugs affected by this price ceiling were produced by at least 35 foreign pharmaceutical companies for the Chinese market.

Determining the price of an imported drug is a bit different. Since the CIF price, shipment documents, customs tax and duty invoice must be submitted when applying for a drug price, the cost determination for imported products is often more transparent than that of local manufactured products. A newly imported drug that has just entered the China market will most likely receive the market price or the same price as a drug in a similar therapeutic area.

## 9.6 ORPHAN DRUGS IN CHINA

Although China currently does not have an official definition for “rare disease,” medical experts estimate that about 10 million Chinese patients have some type of rare disease. In May 2010, the Chinese Medical Association hosted a rare disease definition discussion meeting, and suggested a rare disease to occur in less than 1/500,000 people and 1/10,000 for newborns. However, there has been widespread criticism that this definition is too limited in number.

Rare disease is now given increasing attention in China. On the provincial level, Shanghai covers the treatment of 12 identified rare diseases. This program for rare diseases is similar to a standard medical insurance scheme. Coverage increased in 2012 from 100,000 yuan ($16,100) per person per year to 200,000 yuan ($32,200). However, a

local newspaper reported that treatment for rare disease patients costs an average of 2 million yuan annually ($322,200).

Currently, Shanghai one of the few cities in China embarking on such an initiative. The program is sponsored by Shanghai Civil Affairs Bureau, Shanghai Red Cross and the Health Bureau. In February 2011, the Shanghai Medical Association also set up the Shanghai Rare Disease Society -- a diagnosis and treatment department to promote legislation, research and insurance coverage for rare diseases.

Other local and provincial governments are showing some interest. The Peking Union Medical College Hospital set up a foundation in 2010 to support LAM/TSC patients. In October 2011, Shandong Province founded a Rare Disease Association. Qingdao, in Shandong, approved a 2012 proposal to cover the treatment fees for all diseases -- including rare diseases -- up to 400,000 yuan ($64,400) through the national medical insurance system. At least a portion of hemophilia treatment is covered in many provinces as well.

There is also an increasing number of patient advocacy groups, the main supporters of various rare diseases, such as the China Dolls Association for patients with osteogensis imperfecta. Other groups include the Hemophilia Association of China, LAM China, and the PKU Union. The Rare Disease Office of China Charity Foundation was established with a 2 million yuan ($322,200) grant from Genzyme in 2008. One grassroots group, the Chinese Organization for Rare Disorders, has brought 20,000 people with 33 different rare diseases together on the internet.

On February 28, 2013, 17 medical institutions from 13 different provinces established the China Rare Diseases Prevention and Treatment Alliance -- the country's first national group focusing on rare diseases. The organization will help collect data on rare diseases in China, run epidemiological studies, and work towards better treatments. The lack of experienced doctors in identifying rare diseases in China has led to patients experiencing missed diagnosis, or misdiagnosis of their medical conditions. According to the Alliance, approximately 30% of those with rare diseases need to see 5-10 doctors before receiving a correct diagnosis, while almost 50% are diagnosed incorrectly. Three-fourths of rare disease patients are unable to receive regulated, scientific treatment.

Specific legislation on orphan drugs is still lacking in China. Nevertheless, in 2009, the CFDA published a set of guidelines for Registration of Special New Drugs, with a fast approval process for drugs related to some rare diseases. However, clinical tests would be difficult and time-consuming with the limited number of rare disease patients.

In addition to the new drug registration process discussed earlier in this section, the CFDA offers a priority review process for some categories of drugs, including drugs for rare diseases. These special cases are as follows:

(1) New raw materials, active ingredients, or their preparations made from plants, animals or minerals that have never been marketed in any country

(2) New chemical raw materials, their preparations, and/or biological products that have never been marketed in any country
(3) New drugs used to treat HIV, cancer, or rare diseases that are superior to drugs on the market
(4) New drugs used to treat diseases which do not have effective therapeutic methods

Currently, although Article 45 of the *Provisions for Drug Registration* describes this process, it has not actually been implemented yet. A regulation with more details has been drafted and is currently in the "public comment" phase.

The draft regulation does *not* specify a number of key materials, including how few patients a disease must have to be considered "rare." It *does* state that categories (3) and (4) above will be considered for priority review by an expert panel convened by the CFDA's Center for Drug Evaluation (CDE). The draft also specifies that the following information should be submitted in an application for priority review:

- Clinical trial plan, and summary of any completed clinical trials
- Toxicological and clinical data supporting product safety and efficacy
- Pharmacological data
- Risk management plan and its implementation program
- Other materials as requested by the expert panel

The above data may be submitted in summary form, and should generally not exceed 15 pages.

In addition to this provision, Article 32 of the *Provisions for Drug Registration* specifies that drugs for rare diseases can be registered with fewer clinical trials, or using clinical trials with fewer subjects, than the usual requirements. However, any such reduction must be approved by the CFDA in advance. In 2010, the CFDA reviewed and approved 1,000 registration applications for new drugs, changing dosage forms, generic drugs and imported drugs in accordance with the *Provisions for Drug Registration*. This was a 26.3% application acceptance growth rate from 2009. 89% of these approved applications were chemical drugs.

## 9.7 HEALTH AUTHORITY CONTACT INFORMATION

China Food and Drug Administration (CFDA)
Address: 26 Xuanwumen Xidajie, Beijing, P.R. China, 100053
Fax: +86-010-6831-0909
Email: inquires@sda.gov.cn
Website: http://eng.sfda.gov.cn/WS03/CL0755/

Center for Drug Evaluation (CDE)
Address: 14F, Bldg A, Zhonghuan Plaza, No.70 Zaolinqian St., Xianwu District, Beijing 100053, P.R. China
Phone: +86-010-8397-9589

Fax: +86-010-6858-4181
Email: cde@cde.org.cn

# 10. SINGAPORE

## 10.1 OVERVIEW

Like Hong Kong, Singapore is small but economically advanced, offering a highly-developed healthcare system. The country also serves as an Asian hub for many medical companies. A number of large pharmaceutical companies, such as Pfizer and GlaxoSmithKline, have established a presence in Singapore, and continue to expand their manufacturing and research facilities.

In Singapore, a rare disease is defined as a "life-threatening and severely debilitating illness" affecting less than 20,000 people in its population of 5.5 million (i.e. 0.36% of total Singapore's population).

## 10.2 SINGAPORE HEALTH AUTHORITY

The Health Sciences Authority (HSA) was established in April 2001 to ensure the quality, safety and efficacy of drugs, medical devices, cosmetics, and other health-related products in Singapore. In 2007, a number of existing departments within the HSA were merged into the Health Products Regulation Group (HPRG). This resulted in the introduction of the Health Products Act in 2007. The HPRG's mission is to regulate drugs, innovative therapeutics, medical devices and other health-related products in Singapore to meet appropriate standards of safety, quality and efficacy

## 10.3 ORPHAN DRUG REGISTRATION

A company may apply to the HSA for entry into the Singapore market on a Named Patient Basis. In this case, the importer is required to provide details on the prescribing doctor (who must take responsibility for the use of the drug), patient(s) who will use the drug, and other details on the drug, including its package insert and product label. Each approval for import of drugs on a Named Patient Basis is only valid for 3 months at a time.

Regulations on orphan drugs are classified under the Singapore's Medicines Act. The Medicines Act was gazetted in 1977 to regulate medicinal and related products, including western medicines, Chinese traditional medicines and cosmetic products. The Medicines (Orphan Drugs) (Exemption) Order is a subsidiary legislation under the Medicines Act (chapter 176, Section 9).

Under this Exemption Order, an orphan drug needs to be approved by health authorities either from the drug's country of origin, or from other countries with similar regulatory and product quality standards. Singapore's licensing authorities permit the importation or supply of orphan drugs without a product license, if the orphan drugs are prescribed by medical practitioners to treat rare diseases in their patients, where no other substitute is

available. Orphans drugs must be kept in hospitals and under the responsibility of the medical practitioner or pharmacist appointed by the hospitals.

However, the Exemption Order on Orphan Drugs does not apply to drugs which treat rare diseases that become increasingly common in a span of one year. The Exemption Order also does not apply to orphan drugs which have obtained product license approval by the Singapore licensing authority.

## 10.4 HEALTH AUTHORITY CONTACT INFORMATION

Ministry of Health (MOH)
Address: College of Medicine Building, 16 College Road, Singapore 169854
Phone: +65-6325-9220
Fax: +65-6224-1677
Email: moh_info@moh.gov.sg
Website: http://www.moh.gov.sg

Health Sciences Authority (HSA), Pharmaceutical Division
Address: 11 Outram Road, Singapore 169078
Phone: +65-6213-0838 (general enquiries); +65-6213-0805, +65-6213-0806 (Pharmaceutical Division)
Fax: +65-6213-0749 (Pharmaceutical Division)
Email: hsa_pd_enquiry@hsa.gov.sg (Pharmaceutical Division)
Website: http://www.hsa.gov.sg

# 11. SOUTHEAST ASIA INTRODUCTION

## 11.1 OVERVIEW

For the purpose of this report, Southeast Asia includes the Philippines, Malaysia, Thailand and Vietnam (excluding Singapore).

While Southeast Asia boasts a large population, economic resources are generally limited. The quality and availability of healthcare in Southeast Asia varies between and within countries. Since there are no government-run reimbursement programs in these countries, generally, a patient's family is responsible for paying for all treatment and medication costs, even for chronic illnesses. There are a few private insurance programs, though they tend to place a cap on the total annual cost of treatment. Government employees in some Southeast Asian countries may receive subsidized treatment or medication, though this is also limited and capped at a certain amount. Therefore, unless a patient's family can afford treatment and medication themselves, or obtain charitable donations from outside groups (disease support organizations, associations, etc.) patients are often unable to receive proper treatment or medication in these countries.

## 11.2 DRUG REGISTRATION REQUIREMENTS FOR SOUTHEAST ASIA

| | Required Documents and Information | Phil | Malay | Thai | Viet |
|---|---|---|---|---|---|
| **1** | Authorization Letter to the applicant | √ | √ | X | X |
| **2** | Authorization Letter to the manufacturer (if manufacturer is not product owner) | √ | √ | √ | √ |
| **3** | Summary of product characteristics | √ | √ | √ | √ |
| **4** | Manufacturing plant dossier - Site Master File (for first application only) | √ | √ | √ | √ |
| **5** | Full Formula Product | √ | √ | √ | √ |
| **6** | Product label, outer carton, package insert, product information leaflet | √ (3 sets) | √ (3 sets) | √ (3 sets) | √ (5 sets) |
| **7** | Active raw material specifications | √ | √ | √ | √ |
| **8** | Packaging materials specifications | √ | √ | √ | √ |
| **9** | Certificate of analysis and analytical procedures of active raw materials | √ | √ | √ | √ |
| **10** | Method of manufacturing & AC finished product | √ | √ | √ | √ |
| **11** | Finished product specifications | √ | √ | √ | √ |
| **12** | Analytical methods of the finished product | √ | √ | √ | √ |
| **13** | Certificate of analysis of the finished product | √ | √ | √ | √ |
| **14** | Stability report of finished product: stability testing summary sheet, storage temperature (for at least 3 batches conducted at Climatic Zone IV) | X | X | X | √ |
| **15** | Free Sale Certificate or Certificate of Pharmaceutical Product (Legalized copy from the Consulate) | √ | √ | √ | √ |
| **16** | Validation Documents of critical manufacturing processes | √ | √ | √ | √ |
| **17** | Validation of analytical methods (non-pharmacopoeia) | √ | √ | √ | √ |
| **18** | Expert Report on clinical trial data | √ | √ | √ | √ |
| **19** | Clinical Trial Data (3 published papers) | √ | √ | √ | √ |
| **20** | Product Sample (2 sets) | √ | √ | √ | √ |
| **21** | Registration Status and patent data in other countries | √ | √ | √ | √ |
| **22** | Toxicology and pharmacological data | √ | √ | √ | √ |
| **23** | Optional: Assessment reports from FDA, EMEA, TGA (strong supporting documents) | X | √ | X | X |
| | **Timeframe for approval*** | 12 mo. | 18 mo. | 12-15 mo. | 9-12 mo. |

**Note: Time to register orphan drugs may be faster than the timeframe above for a new drug registration.*

# 12. PHILIPPINES

## 12.1 OVERVIEW

The Philippine pharmaceutical market is largely comprised of imported drugs and is valued at $3.4 billion. The US has a limited presence in the market, holding less than 8% of the market share; the U.K., Germany, France and Switzerland each hold around 10%. However, since the Philippine Food and Drug Administration (FDA) has adopted US Pharmacopoeia standards, US pharmaceuticals should continue to have good market potential.

The Philippines defines a disease as "rare" if it is a genetic disorder which affects less than 1 in 20,000 people in the country. There is currently little financial and medical support for Filipinos afflicted with rare disease. There is also lack of information and experience by doctors to provide accurate diagnosis and treatment for the patients. As of March 2011 there were approximately 30 rare diseases officially registered, affecting 244 patients -- classified as having 'rare inborn errors of metabolism.' However, this does not include those who have not been diagnosed, those seeing private doctors, and those who do not seek diagnosis or treatment due to the stigma of having a rare disease. As rare diseases affect only a small percentage of the country's population, there is little interest among research institutions in the Philippines to study these diseases in detail.

## 12.2 PHILIPPINE HEALTH AUTHORITY

The Philippine FDA was established to ensure the safety, efficacy, purity and quality of health products in the Philippines. The *Food, Drug and Cosmetic Act* provides the regulations to monitor food, drugs, medical devices, diagnostic reagents, cosmetics and household hazardous substances in the Philippines.

In July 2010, the Rare Diseases Act of the Philippines was filed at the country's annual Congress to be passed as law. The Act seeks to create an Office of Rare Diseases within the Department of Health and to encourage the research and development on rare diseases. Through this Act, government incentives will also be provided for the manufacture or importation of medical products to treat rare diseases. The bill did not pass and was re-filed in the Senate. A similar bill was filed in the House of Representatives. In 2010, a separate Orphan Diseases Act was also proposed. None of these bills has been passed.

## 12.3 ORPHAN DRUG REGISTRATION PROCESS

Similar to Singapore's Named Patient Basis scheme, the Philippines has a *Compassionate Use* scheme, allowing an orphan drug to be imported on a named-patient basis prior to receiving product registration. The *Compassionate Use* application process takes 3-6 months.

Coverage is generally intended for patients suffering from severe, life-threatening conditions for which there is no other option with good prospects, such as AIDS, cancer, and others.

The *Compassionate Use* scheme requires an applicant to obtain a *Compassionate Special Permit* (CSP) from the FDA Director, which grants "restrictive use of an unregistered drug." The CSP may only be granted to a Specialized Institution (SI) or Specialty Society (SS).

Requirements on the part of the SI or SS:

- An estimate of the total amount of the product needed for one year.
- A certificate showing that the product is currently registered in the country of origin
- A waiver of FDA responsibility from any damage or injury arising from the use of the unregistered drug, signed by the responsible official of the SI or SS.
- The specialists must submit clinical study reports on each patient to the drug manufacturer by the end of each year. (The drug manufacturer is responsible for reporting to the FDA the total annual drug volume actually imported into the Philippines.)

The CSP is issued with the following specifications:

- A named licensed establishment
- Certain types of patients
- Specific volumes/dosages
- A specified time period

## 12.4 HEALTH AUTHORITY CONTACT INFORMATION

Food and Drug Administration (FDA)
Address: Civic Drive, Filinvest Corporate City, Alabang, Muntinlupa City, Philippines 1781
Phone: +63-2-857-1990; +63-2-165-332
Fax: +63-2-807-0751; +63-2-807-8511
Email: info@fda.gov.ph
Website: http://www.fda.gov.ph

Department of Health (DOH)
Address: San Lazaro Compound, Tayuman, Sta. Cruz, Manila, Philippines 1003
Phone: +63-2-743-8301; +63-2-651-7800
Fax: +63-2-711-6744
Email: info@doh.gov.ph
Website: http://www.doh.gov.ph

## 12.5 ORPHAN DRUG ASSOCIATIONS

Philippine Society for Orphan Disorders
Address: Rm 206, Greenhills Mansion, #37 Annapolis St., Greenhills, San Juan, Metro Manila, Philippines 1500
Phone: +63-2-661-8935
Email: into@psod.org.ph
Website: http://www.psod.org.ph/

*PSOD is a nonprofit organization founded in 2006 by doctors and family members of rare disease patients. The group works to help both patients and their families. PSOD also runs community awareness campaigns, counseling for grief due to rare diseases, and seminars for taking care of patients with rare diseases.*

# 13. MALAYSIA

## 13.1 OVERVIEW

The pharmaceutical market in Malaysia is valued at more than $3.1 billion and growing steadily at 6-8% annually. While there are over 50 registered drug manufacturers in Malaysia, the country still imports most of its pharmaceuticals, with the US, Japan, and Germany as its largest importers. The Malaysian government considers its medical industry to be one of its top priorities and continually strives to improve regulations and implement new schemes.

Malaysia defines "rare disease" as one which affects less than 1 in 4,000 people in the country (which has a population of 30 million). These are mainly genetic disorders which are prevalent among children. Educational resources and support groups for rare diseases are limited in Malaysia. This is also compounded by the lack of doctors trained in early intervention programs and treatment of these diseases.

## 13.2 MALAYSIA HEALTH AUTHORITY

Pharmaceuticals are regulated by the Drugs Control Authority (DCA) in Malaysia, under the *Control of Drugs and Cosmetics Regulations 1984*. The DCA is part of the National Pharmaceutical Control Bureau, itself under the Malaysian Ministry of Health. The DCA is managed by the Director General of Health, Director of Pharmaceutical Services, Director of the National Pharmaceutical Control Laboratory, and seven other appointed members. The main responsibility of the DCA is to ensure the safety, quality and efficacy of pharmaceuticals in Malaysia. The DCA's duties include (1) reviewing registration applications for drugs and cosmetics, (2) licensing importers, manufacturers and wholesalers, (3) post-marketing safety surveillance, and (4) adverse drug reaction (ADR) monitoring.

According to the DCA, *any drug in a pharmaceutical dosage form, intended to be used, or capable or purported or claimed to be capable of being used on humans or any animals, whether internally or externally, for a medicinal purpose* is required to be registered with the DCA. This includes products which alleviate, treat or cure diseases, products that diagnose a disease, anesthetics, and products that maintain, modify, prevent, restore or interfere with normal physiological functions. The regulation does not apply to diagnostic agents and test kits for laboratory use; non-medicated medical and contraceptive devices; non-medicated bandages and surgical dressings; and instruments, apparatus, syringes, needles, sutures and catheters.

## 13.3 DRUG REGISTRATION OVERVIEW

In Malaysia, only local distribution companies can submit a drug registration application. Therefore, foreign companies with no local presence in Malaysia must designate a

Market Authorization Holder (MAH) as their local representative. A MAH is responsible for submitting the product application, as well as ensuring the quality, safety and efficacy of the product.

There are three types of applications for drug approval in Malaysia: (1) application for an innovator product, (2) application for a generic drug, and (3) abridged application. An application for an innovator drug includes drugs containing a new chemical or biological entity, or a new combination of existing chemicals/biologicals. Changes in product composition or characteristics (such as color, shade, flavor, fragrance or shape) will also require a new registration application. Conversely, a change in product name, specifications, packaging, indications, labeling, package insert, product literature, or excipients only requires an abridged application, which must be submitted to the DCA prior to making the change(s). (Any products imported for the purpose of clinical trials are not required to be registered with the DCA, but should have a clinical trial license. If a product will be manufactured locally for a clinical trial, a clinical trial exemption should be obtained from the DCA.)

The product registration procedure must be completed online at www.bpfk.gov.my. The product registration application will require documents and information such as the following.

- Letter of authorization from the product owner, as well as the contract manufacturer, if any, stating the product name, manufacturer's name and manufacturer's address.
- Certificate of Pharmaceutical Product (CPP) from the pharmaceutical authority in the country of origin. (If a CPP is not available, a GMP certificate or manufacturing license is generally acceptable along with either a (1) CPP from the country of the product owner or (2) CPP from country of release.)

A separate application is required for each product to be registered. The DCA's application review process follows a queue system, which is divided by product type: New Chemical Entity (NCE), biotechnology products, generic products, abridged applications and traditional products.

Once the application review process is complete, the DCA will notify the MAH of its decision via e-mail. When a product is approved, the DCA will assign a registration number to the product, which is associated with the product's name, composition, characteristics, origin, manufacturer and MAH. The registration number cannot be used with any other product. Product registration is valid for five years; renewal applications should be submitted approximately six months prior to the expiration date of the registration.

Although there is no specific process for orphan drug registration in Malaysia, if a product is used to treat a serious or life-threatening disease, the DCA may expedite the review process for that particular product. Certain drugs can be permitted on a named-patient basis. To do so, the applicant must submit an application in writing to the

Ministry of Health which states the product name and justification for the doctor to use the drug.

## 13.4 HEALTH AUTHORITY CONTACT INFORMATION

Ministry of Health
Address: Block E1, E6, E7 and E10, Parcel E, Federal Government Administration Center, 62590, Putrajaya, Malaysia
Phone: +60-3-8000-8000
Fax: +60-3-8888-6187
Email: kkm@moh.gov.my
Website: http://www.moh.gov.my

National Pharmaceutical Control Bureau (and Drug Control Authority)
Address: No. 36, Jalan Universiti, 46200 Petaling Jaya, Selangor Darul Ehsan, Malaysia
Phone: +60-3-7883-5400; +60-3-7883-5409
Fax: +60-3-7956-2924; +60-3-7956-7075
Email: admin@bpfk.gov.my
Website: http://www.bpfk.gov.my

## 13.5 ORPHAN DRUG ASSOCIATIONS

Malaysian Rare Disorders Society
Address: 16 Lorong 5/10D, 46000 Petaling Jaya, Selangor, Malaysia
Phone: +0-19-771-4543
Fax: +60-3-7958-8459; +60-3-7949-2067
Email: info@mrds.org.my
Website: http://www.mrds.org.my/

*MRDS was founded in 2004 and is a volunteer organization that advises families of children with rare diseases and helps patients find specialists to provide treatment. MRDS was founded with the help of the Universiti Malaya Medical Center's Genetic Unit.*

# 14. THAILAND

## 14.1 OVERVIEW

The Thai Food and Drug Administration (FDA), under the Ministry of Public Health (MOPH), is responsible for protecting the health of consumers by ensuring the safety, quality and efficacy of health products, including food, pharmaceuticals, medical devices and cosmetics, in Thailand. The FDA has five main areas of focus: (1) pre-marketing, (2) post-marketing, (3) product surveillance, (4) product education for the consumer and (5) cooperation with other health-related agencies. The FDA has close to 500 staff members who run the agency, including pharmacists, nutritionists, lawyers and other health professionals.

## 14.2 DRUG REGISTRATION OVERVIEW

The Thai FDA regulates pharmaceuticals through the *Drug Act of B.E 2530*. The *Drug Act* requires a company to obtain a license in order to import, sell or manufacture drugs in Thailand. Specifically, licenses are required for the following activities.

- Importing, manufacturing or selling medicines
- Acting as a wholesaler of medicines
- Selling medicines in sealed packages that are not classified as dangerous or specially-controlled medicines
- Importing, manufacturing or selling traditional medicines
- Selling veterinary medicines in sealed packages

Thailand's product registration process has been set up to ensure the safety, quality and efficacy of pharmaceutical products in Thailand. According to the *Drug Act*, for product registration purposes, pharmaceuticals are divided into three categories: (1) new medicines, (2) generics, and (3) new generics. New drugs are classified as products with new chemicals, chemical combinations, indications, delivery systems or dosage forms. New generics include medicines with the same active ingredients, doses and dosage forms as those of new compounds registered after 1992. Product registration licenses are valid for 5 years.

New drugs will require a complete dossier for registration, while generics will only require a dossier containing product details, manufacturing and quality control information. New generic drug applications will need to include bioequivalence studies in addition to the requirements for a generic drug application. The Drug Control Division of the MOPH, or a provincial public health office, is responsible for reviewing and issuing registration licenses. Prior to granting a license, the health authority may conduct an inspection of the manufacturing site to ensure GMP compliance.

The Medical Sciences Department under the MOPH is the main authority responsible for ensuring the quality and safety of drugs on the market in Thailand. Samples of products on the market are regularly tested at the Medical Sciences Department laboratory. Other

local laboratories also conduct post-marketing surveillance for the MOPH by performing the following measures:

- Safety monitoring of new drugs on the market
- Handling product complaints
- Monitoring drugs on the market for unexpected health risks
- Informing the public of risks posed by specific drugs; investigate the cause of the risk; if necessary, remove the drug from the market
- Inspecting manufacturing sites for GMP compliance
- Monitoring manufacturing process changes

## 14.3 ORPHAN DRUG SUMMARY

Rare diseases in Thailand are mostly endocrinology and metabolism diseases. As in the other South East Asian countries, Thailand's rare disease patients lack both the essential information on their medical conditions and accessibility to orphan drug treatment.

Only a few rare disease patients in Thailand have access to state treatment. Outside of Bangkok, there is a serious shortage of specialists and drugs, meaning that very few patients have access to medication. Thailand has fewer than 15 medical geneticists -- for a country of 67 million. Infant screening tests and orphan drugs are not widely accessible, and these treatments are not included on the country's National Drug List or covered by the universal healthcare system. This makes the cost of treatment prohibitively expensive for most.

However, the health authorities are slowly developing strategies and approaches to support the importation of orphan drugs, such as a fast-track registration process and the importation of certain orphan drugs prior to product registration.

## 14.4 HEALTH AUTHORITY CONTACT INFORMATION

Ministry of Public Health
Address: 1st Floor, Building 1, Tivanond Road, Nonthaburi 11000, Thailand
Phone: +66-2590-1000
Fax: +66-2590-2802
Email: webmaster@health.moph.go.th
Website: http://eng.moph.go.th/

Food and Drug Administration, Drug Control Division
Address: Thanon Tiwanond, Amphoe Muang, Nonthaburi 11000, Thailand
Phone: +66-2590-7160; +66-2590-7171
Fax: +66-2591-8390; +66-2591-8489; +66-2590-7170
Email: drug@fda.moph.go.th
Website: http://www.fda.moph.go.th/eng/index.stm

# 15. VIETNAM

## 15.1 OVERVIEW

While the healthcare industry in Vietnam is still developing, it is one of the faster growing markets in the medical industry. The Vietnam pharmaceutical market is worth more than $3.2 billion. More than 200 foreign pharmaceutical companies are registered in Vietnam, making up over 50% of the country's market share. In an attempt to improve the overall pharmaceutical market in Vietnam, the country's National Assembly approved a new Pharmaceutical Law in 2005. The law is intended to help develop the domestic pharmaceutical industry in Vietnam and also address drug pricing, which has been an issue of constant battle between the drug companies and government in Vietnam for a number of years.

## 15.2 DRUG REGISTRATION OVERVIEW

The Ministry of Health (MOH) regulates pharmaceuticals in Vietnam, though the regulatory environment can often be unclear and inconsistent. Regulations are frequently implemented on a case-by-case basis, with little overall coordination. Partially-regulated situations, or regulations that are clearly contradictory, are not unheard of. Moreover, it can be difficult to determine what is permitted in Vietnam and what is illegal. Therefore, foreign companies can face numerous challenges when attempting to navigate the pharmaceutical sector in Vietnam. Foreign companies are more likely to succeed in the market when paired up with a company or personnel who have previous experience in this sector.

The definition of "pharmaceutical products" is somewhat ambiguous under Vietnamese law. The MOH only states that pharmaceutical products are *products intended for human consumption for the purpose of prevention, treatment, relief or diagnosis of diseases, or for the modification of physiological functions*. Any pharmaceutical products manufactured, sold or distributed in Vietnam must first be registered with the MOH. The majority of the product application can be completed in English.

The MOH reviews the application and if they approve it, they will issue the approval license (locally known as a visa). Generally, the review and approval process takes 3-4 months. Additionally, in 2004, the MOH established a drug review panel to review applications for the approval of drugs not yet registered for distribution in Vietnam. The MOH intended for this panel, which meets once a week, to help speed up the application review process. Product registration is valid for 5 years.

Some product approval processes will also include product sample analysis, though this occurs only in about ten percent of all application processes. In this case, the product application and sample will be forwarded to the Vietnam Institute of Quality Control. The Institute will analyze the sample and compare the results with the Certificate of Analysis

included in the registration application. The applicant is responsible for paying the testing fee; the amount depends on the number and complexity of the test(s).

In Vietnam, special import approvals can be granted in some cases for non-registered products. The 2001 Regulation on Drug Registration specifically notes, "In special cases (drugs for epidemic and disasters relief and orphan drugs) the sale and consumption of un-registered drugs shall be specifically considered and approved by the Ministry of Health." Compassionate use of drugs is also possible.

As in other Southeast Asian countries, patients with rare diseases often do not seek treatment due to local superstitions. In early 2014, one case involved an 11 year old girl with Lyell's syndrome, a rare skin disorder. The girl's parents were persuaded by a local fortune teller to leave her in the jungle because "jungle ghosts have eaten her heart and liver, [and] there's no way to cure her." Local authorities ultimately brought the girl to the hospital where she received treatment.

## 15.3 HEALTH AUTHORITY CONTACT INFORMATION

Ministry of Health
Address: 138A Giảng Võ, Ba Đình, Hà Nội, Vietnam
Phone: +84-4-6273-2273
Fax: +84-4-3846-4051
Email: banbientap@moh.gov.vn
Website: http://www.moh.gov.vn/

Drug Administration of Vietnam
Address: 138A Giảng Võ, Ba Đình, Hà Nội, Vietnam
Phone: +84-4-3736-6483
Fax: +84-4-3823-4758
Email: cqldvn@ moh.gov.vn
Website: http://www.dav.gov.vn

## 15.4 ORPHAN DRUG ASSOCIATIONS

Vietnam Center for Genetic Analysis and Technologies
Address: E3-108, Vinh Phuc, Ba Đinh, Hanoi, Vietnam;
278 Thuy Khue, Hanoi, Vietnam
Phone: +84-4-3728-2496
Fax: +84-4-3754-3391
Email: trungtame3@yahoo.com
Website: http://phantich-adn.com/english/index_en.htm

*Established to improve the diagnosis of genetic diseases in Vietnam.*

# 16. SALES AND MARKETING OF ORPHAN DRUGS

## 16.1 INTRODUCTION

Prior to pursuing orphan drug designation and marketing approval in an Asian country, a drug company should conduct market research to ensure commercial viability of the product there. In the case of an orphan drug, it is essential that a company determine the potential number of patients and consider other important variables such as competing products, product reimbursement and disease awareness.

## 16.2 PREPARING A SALES FORECAST

Through the preparation of a sales forecast, a drug company can analyze their potential sales and marketing situation. Some of the costs and issues that should be accounted for are as follows:

- Product registration costs (Is there a distributor in the country that is willing to absorb these costs?)
- Clinical trial costs (These costs could be partially absorbed by an orphan drug financial aid grant from the country's health authority.)
- Number of current vs. potential patients
- Disease awareness in the country
- Competitors
- Cost of the product
- Marketing exclusivity

It is important to remember that a named-patient program, which is available in a number of Asian countries, would allow for product sales prior to the completion of product registration. While sales are limited under a named-patient program, the drug company is able to introduce the product to patients and establish relationships with doctors.

## 16.3 IN-COUNTRY SUPPORT

Although there are thousands of rare diseases and numerous groups and organizations to support patients, the awareness of rare diseases can often be low, especially in Asia. While Asia's population is large, suggesting the potential for a large number of patients with rare diseases, these populations tend to lie in poor and less advanced areas in the region. Therefore, the development of in-country support and disease awareness is a crucial aspect of the orphan drug marketing process in Asia.

It is often beneficial to conduct market research in order to ascertain how other orphan drugs were introduced into the country and how support was established. Did the orphan drug company contact leading doctors or key opinion leaders? Were conferences or formal meetings held? Did a rare disease group or organization provide support? How are the drugs dispensed? Some other ways of increasing awareness are as follows:

- Face-to-face discussions with doctors and medical professionals
- Ask doctors to publish papers in medical journals (international, regional or domestic)
- Establish a group/association/organization specifically addressing the disease
- Establish local support groups for the families of patients; link these groups to a regional/international association/organization
- Create a database of local/regional doctors or medical professionals who can see patients and make visits to discuss the disease/condition

Ensure that information about your new orphan product is available to doctors, hospitals, organizations, etc. An orphan drug company should be active in increasing awareness *and* educating the medical community about the disease their drug treats. In turn, this will maximize the number of diagnosed cases.

Finally, it is important to consider the cost of the medication. If your drug is expensive and the majority of patients diagnosed with the disease would not be able to afford treatment, ensure that charitable institutions would be able to provide significant financial support. Generally, expensive drugs are not sold in Southeast Asia if suitable alternatives already exist.

## 17. CONCLUSION

Drug companies that have already received product approval in the US or Europe should have an easier time when applying for orphan drug approval in Asia. However, each Asian country is unique and has a distinctive orphan drug approval process. Developed Asian countries, including Japan, Korea, Taiwan, Singapore and Hong Kong, have had more experience with rare diseases, orphan drugs and reimbursement for such drugs. In contrast, the developing Asian countries, including the Philippines, Malaysia, Thailand and Vietnam, have had less experience with rare diseases or orphan drugs, and generally do not offer public reimbursement.

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