ORPHAN DRUGS IN ASIA
2017

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

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TABLE OF CONTENTS

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

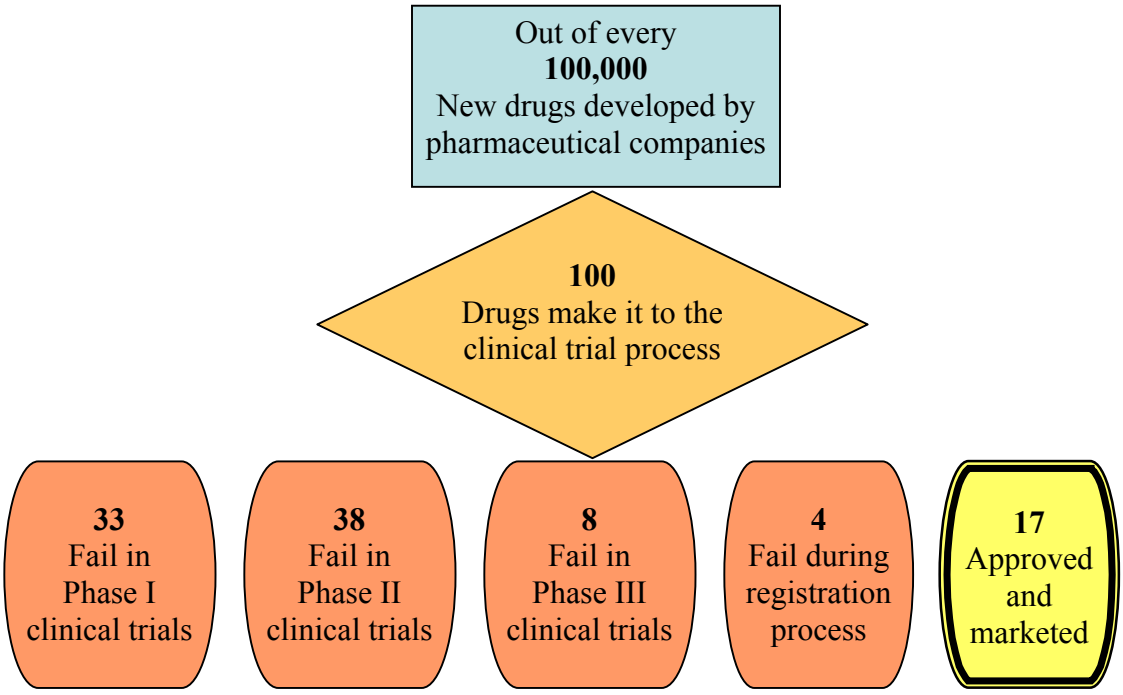
significant financial loss. Therefore, in the past, many drugs for rare diseases were developed as a response to a public health need rather than for economic purposes or financial gain by drug companies.

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): 301-796-8682
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
Website: https://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.

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 2010 TO JULY 2017)

Marketing Approval	Generic Name	Trade Name	Designation (may be abbreviated)	Orphan Designation	Company
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 Plc
3/18/2010	Carglumic Acid	Carbaglu	Adjunctive therapy for acute hyperammonemia treatment and manitenance therapy for chronic hyperammonemia	1/20/1998	Orphan Europe SARL
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.
5/24/2010	Alglucosidase alfa	Myozyme Lumizyme	Treatment of glycogen storage disease type II for patients 8 years and older	08/19/1997	Genzyme Corporation
7/28/2010	Glycopyrrolate	Cuvposa	Treatment of reducing chronic drooling in young patients with neurologic conditions associated with drooling problems	6/9/2006	Shionogi, Inc.
9/14/2010	Pegloticase	Krystexxa	Treatment of chronic gout in adult patients	2/21/2001	Horizon Pharma Rheumatology, LLC
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.

Marketing Approval	Generic Name	Trade Name	Designation (may be abbreviated)	Orphan Designation	Company
10/29/2010	Everolimus	Afinitor	Treatment of subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis	6/8/2009	Novartis Pharmaceuticals Corporation
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	AMAG Pharma USA, Inc.
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.
3/11/2011	Crizotinib	Xalkori	Treatment of ALK-positive, MET-positive, or ROS-positive non-small cell lung cancer	09/13/2010	Pfizer, Inc.
3/25/2011	Ipilimumab	Yervoy	Treatment of unresectable or metastatic melanoma	6/3/2004	Bristol-Myers Squibb Company
3/29/2011	Peginterferon alfa-2b	Sylatron	Adjuvant treatment of melanoma with microscopic or gross nodal involvement	4/9/2008	Schering-Plough Corporation
4/6/2011	Vandetanib	Caprelsa(R)	Treatment of asymptomatic or progressive medullary thyroid cancer	10/21/2005	Genzyme Corporation
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
6/16/2011	Romidepsin	Istodax	Treatment of non-Hodgkin T-cell lymphomas	9/30/2004	Celgene Corporation
7/29/2011	Coccidioidin SD Skin Test Antigen	Spherusol	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.

Marketing Approval	Generic Name	Trade Name	Designation (may be abbreviated)	Orphan Designation	Company
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 Plc
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.
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	Novartis Phamaceuticals Corporation
4/26/2012	Everolimus	Afinitor	Treatment of tuberous sclerosis complex	6/8/2009	Novartis Pharmaceuticals Corporation

Marketing Approval	Generic Name	Trade Name	Designation (may be abbreviated)	Orphan Designation	Company
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	Arbor Pharmaceuticals, LLC
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	Baxalta US, Inc
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	Leadiant Biosciences, Inc.
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.

Marketing Approval	Generic Name	Trade Name	Designation (may be abbreviated)	Orphan Designation	Company
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
1/23/2013	Deferasirox	Exjade	Treatment of chronic iron overload in alpha-thalassemia	2/24/2015	Novartis Pharmaceuticals Corporation
1/24/2013	Factor XIII concentrate (human)	Corifact	Treatment of congenital factor XIII deficiency	1/16/1985	CSL Behring LLC
1/25/2013	Imatinib	Gleevec	Treatment of Philadelphia-positive acute lymphoblastic leukemia	10/11/2005	Novartis Pharmaceuticals Corporation
1/29/2013	Mipomersen	Kynamro	Reduce cholesterol in patients with homozygous familial hypercholesterolemia (HoFH)	5/23/2006	Kastle Therapeutics, LLC
2/1/2013	Glycerol phenylbutyrate	Ravicti	Use as an adjunctive therapy for chronic management of urea cycle disorders (UCDs)	4/27/2009	Horizon Pharma USA, 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.
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)	Heptavalent Botulism AntiToxin	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.

Marketing Approval	Generic Name	Trade Name	Designation (may be abbreviated)	Orphan Designation	Company
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 LLC
4/30/2013	Cysteamine enteric coated	Procysbi	Management of nephropathic cystinosis in adults and children ages 6 years and older	10/24/2006	Horizon Pharma USA, 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	Novartis Pharmaceuticals Corporation
5/29/2013	Dabrafenib	Tafinlar	Treatment of unresectable or metastatic melanoma with BRAF V600E mutation	1/12/2011	Novartis Pharmaceuticals Corporation
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	Baxalta US, Inc.
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.
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.

Marketing Approval	Generic Name	Trade Name	Designation (may be abbreviated)	Orphan Designation	Company
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 LLC
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	Baxalta US, Inc.
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	Novartis Pharmaceuticals Corporation
1/9/2014	Dabrafenib	Tafinlar	Combination treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations	9/20/2012	Novartis Pharmaceuticals Corporation
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.

Marketing Approval	Generic Name	Trade Name	Designation (may be abbreviated)	Orphan Designation	Company
2/18/2014	Droxidopa	Northera	Treatment of adult patients with symptomatic neurogenic orthostatic hypotension	1/17/2007	Lundbeck LLC
2/24/2014	Metreleptin	Myalept	Treat complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy	8/22/2001	Aegerion Pharmaceuticals
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.
3/28/2014	Coagulation factor IX (recombinant), Fc fusion protein	Alprolix	Control and prevention of hemorrhagic episodes in patients with hemophilia B (congenital factor IX deficiency or Christmas disease)	10/30/2008	Bioverativ Therapeutics, Inc.
3/28/2014	Ecallantide	Kalbitor	Treatment of angioedema	2/4/2003	Dyax Corporation
4/4/2014	Ethiodized oil injection	Lipiodol	Management of patients with known hepatocellular carcinoma (HCC)	9/26/2013	Guerbet LLC
4/17/2014	Ofatumumab	Arzerra	Treatment of chronic lymphocytic leukemia	3/10/2009	Novartis Pharmaceuticals Corporation
4/21/2014	Ramucirumab	Cyramza	Treatment of gastric cancer	2/16/2012	Eli Lilly and Company
4/23/2014	Siltuximab	Sylvant	Treatment of Castleman's disease	5/26/2006	Janssen Research & Development, LLC
4/28/2014	Mercaptopurine oral solution	Purixan	Treatment of acute lymphoblastic leukemia in pediatric patients	8/20/2012	Nova Laboratories Limited
4/29/2014	Ceritinib	Zykadia	Treatment of patients with non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase(ALK)-positive	9/27/2013	Novartis Pharmaceuticals Corporation
6/6/2014	Antihemophilic factor (recombinant), Fc fusion protein	Eloctate	Treatment of hemophilia A	11/23/2010	Bioverativ Therapeutics, Inc.
6/13/2014	Technetium Tc 99m tilmanocept	Lymphoseek	Use in sentinel lymph node detection (SLN) with a hand-held gamma-counter, with scintigraphic imaging, in patients with cancer of the head and neck	9/17/2014	Navidea Biopharmaceuticals

Marketing Approval	Generic Name	Trade Name	Designation (may be abbreviated)	Orphan Designation	Company
7/2/2014	Coagulation factor VIIa (recombinant)	Novoseven Rt	Treatment of bleeding episodes in Glanzmann's thrombasthenia	6/18/2004	Novo Nordisk Inc.
7/3/2014	Belinostat	Beleodaq	Treatment of peripheral T-cell lymphoma (PTCL)	09/03/2009	Spectrum Pharmaceuticals, Inc.
7/16/2014	C1-esterase inhibitor (recombinant)	Ruconest	Treatment of (acute attacks of) angioedema caused by hereditary or acquired C1-esterase inhibitor deficiency	2/23/1999	Pharming Group N.V.
7/22/2014	Dantrolene sodium suspension for injection	Ryanodex	Treatment of malignant hyperthermia syndrome	8/16/2013	Eagle Pharmaceuticals, Inc.
7/23/2014	Idelalisib	Zydelig	Treatment of follicular lymphoma	9/26/2013	Gilead Sciences, Inc.
7/23/2014	Idelalisib	Zydelig	Treatment of chronic lymphocytic leukemia and small lymphocytic lymphoma	10/15/2013	Gilead Sciences, Inc.
7/28/2014	Ibrutinib	Imbruvica	Treatment of chronic lymphocytic leukemia	4/6/2012	Pharmacylics, Inc.
8/1/2014	Alglucosidase alfa	Myozyme Lumizyme	Treatment of glycogen storage disease type II for patients of all ages	8/19/1997	Genzyme Corporation
8/19/2014	Eliglustat	Cerdelga	Treatment of type I Gaucher disease	9/17/2008	Genzyme Corporation
8/26/2014	Eltrombopag	Promacta	Treatment of aplastic anemia	11/8/2013	Novartis Pharmaceuticals Corporation
9/4/2014	Pembrolizumab	Keytruda	Treatment of Stage IIB through IV malignant melanoma	11/19/2012	Merck, Sharpe & Dohme Corporation
9/23/2014	Adalimumab	Humira	Treatment of pediatric Crohn’s disease	10/19/2006	AbbVie, Inc.
9/23/2014	Adalimumab	Humira	Treatment of juvenile rheumatoid arthritis	3/21/2005	AbbVie, Inc.
10/8/2014	Bortezomib	Velcade	Treatment of mantle cell lymphoma	5/30/2012	Millenium Pharmaceuticals, Inc.
10/15/2014	Nintedanib	Ofev	Treatment of patients with idiopathic pulmonary fibrosis	6/29/2011	Boehringer Ingelheim Pharmaceuticals, Inc.
10/15/2014	Pirfenidone	Esbriet	Treatment of idiopathic pulmonary fibrosis	3/5/2004	Genentech
10/23/2014	Antihemophilic factor (recombinant)	Obizur	Treatment and prevention of episodic bleeding in patients with inhibitor antibodies to human coagulation factor VIII	3/16/2004	Baxalta US, Inc.
11/5/2014	Ramucirumab	Cyramza	Treatment of gastric cancer	2/16/2012	Eli Lilly and Company
11/14/2014	Bevacizumab	Avastin	Treatment of fallopian tube carcinoma	11/23/2010	Genentech

Marketing Approval	Generic Name	Trade Name	Designation (may be abbreviated)	Orphan Designation	Company
11/14/2014	Bevacizumab	Avastin	Therapeutic treatment of patients with ovarian cancer	2/9/2006	Genentech
11/14/2014	Bevacizumab	Avastin	Treatment of primary peritoneal carcinoma	11/2/2010	Genentech
11/21/2014	Cinacalcet	Sensipar	Treatment of hypercalcemia	4/30/2010	Amgen, Inc.
12/3/2014	Blinatumomab	Blincyto	Treatment of acute lymphocytic leukemia	5/16/2008	Amgen, Inc.
12/4/2014	Ruxolitinib	Jakafi	Treatment of polycythemia vera	3/26/2010	Incyte Corporation
12/5/2014	Denosumab	Xgeva	Treatment of hypercalcemia in malignancy	9/11/2013	Amgen, Inc.
12/12/2014	Aripiprazole	Abilify	Treatment of Tourette's syndrome	1/25/2006	Otsuka Pharmaceutical Ltd.
12/15/2014	Pasireotide	Signifor	Treatment of acromegaly	8/25/2009	Novartis Pharmceutical Corporation
12/16/2014	Lanreotide Acetate	Somatuline Depot	Treatment of neuroendocrine tumors	8/25/2011	Ipsen Biopharmaceuticals, Inc.
12/19/2014	Olaparib	Lynparza	Treatment of ovarian cancer	10/16/2013	AstraZeneca Pharmaceuticals LP
12/22/2014	Nivolumab	Opdivo	Treatment of Stage IIb to IV melanoma	1/23/2013	Bristol-Myers Squibb Company
1/19/2015	Levodopa	Duodopa	Treatment of late stage Parkinson's disease	1/18/2000	AbbVie, Inc.
1/13/2015	Phoxilium	--	For use as a replacement solution in patients undergoing continuous renal replacement therapy	2/14/2014	Gambro Renal Products, Inc.
1/23/2015	Parathryoid hormone	Natpara	Treatment of hypoparathyroidism	8/31/2007	Shire-NPS Pharmaceuticals, Inc.
1/29/2015	Ibrutinib	Imbruvica	Treatment of Waldenstrom's macoglobulinemia	10/15/2013	Pharmacylics, Inc.
2/13/2015	Lenvatinib	Lenvima	Treatment of follicullar, medullary, anaplastic, and metastatic or locally advanced papillary thyroid cancer	12/27/2012	Eisai, Inc.
2/17/2015	Lenalidomide	Revlimid	Treatment of multiple myeloma	9/20/2001	Celgene Corporation
2/23/2015	Panobinostat	Farydak	Treatment of multiple myeloma	8/20/2012	Novartis Pharmaceuticals Corporation
3/6/2015	Isavuconazonium sulfate	Cresemba	Treatment of zygomycosis	10/25/2013	Astellas Pharma Inc.
3/6/2015	Isavuconazonium sulfate	Cresemba	Treatment of invasive aspergillosis	5/6/2013	Astellas Pharma Inc.
3/10/2015	Dinutuximab	Unituxin	Treatment of neuroblastoma	12/20/2010	United Therapeutics Corporation

Marketing Approval	Generic Name	Trade Name	Designation (may be abbreviated)	Orphan Designation	Company
3/17/2015	Cholic acid	Cholbam	Treatment of inborn errors of cholesterol and bile acid synthesis and metabolism	3/17/2015	Retrophin
3/24/2015	Anthrax immune globulin (human)	Anthrasil	Treatment of inhalational anthrax	7/29/2008	Cangene Corporation
3/20/2015	Filgrastim	Neupogen	Treatment of subjects at risk of developing myelosuppression after a radiological or nuclear incident	11/20/2013	Amgen, Inc.
5/6/2015	Crotalidae (pit viper) Immune F(ab')2 (Equine)	Anavip	Treatment of envenomation by Crotaline snakes	1/29/2004	Rare Disease Therapeutics
5/28/2015	Sirolimus	Rapamune	Treatment of lymphangioleiomyomatosis	10/31/2012	Pfizer, Inc.
7/2/2015	Lumacaftor	Orkambi	Treatment of cystic fibrosis	6/30/2014	Vertex Pharmaceuticals, Inc.
7/10/2015	Tacrolimus	Envarsus Xr	Prophylaxis of organ rejection in patients receiving allogeneic kidney transplant	12/20/2013	Veloxis Pharmaceuticals, Inc.
7/13/2015	Gefitinib	Iressa	Treatment of epidermal growth factor receptor mutation-positive non-small cell lung cancer	7/13/2015	AstraZeneca Pharamceuticals LP
8/7/2015	Dichlorphenamide	Keveyis	Treatment of periodic paralyses	9/2/2010	Strongbridge US, Inc.
8/14/2015	Cysteamine enteric coated	Procysbi	Treatment of cystinosis	10/24/2006	Horizon Pharma USA, Inc.
8/17/2015	Brentuximab vedotin	Adcetris	Treatment of Hodgkin's lymphoma	1/30/2007	Seattle Genetics, Inc.
8/27/2015	Evolocumab	Repatha	Treatment of homozygous familial hypercholesterolemia	9/23/2013	Amgen, Inc.
9/4/2015	Uridine triacetate	Vistogard	Treatment of hereditary orotic aciduria	8/9/2013	Wellstat Therapeutics, Inc.
9/9/2015	Adalimumab	Humira	Treatment of moderate to severe hidradenitis suppurativa (Hurley stage 2 and Hurley stage 3 disease)	5/13/2015	AbbVie, Inc.
10/9/2015	Combination of nivolumab and ipilimumab	Opdivo + Yervoy	Treatment of Stage IIb to Stage IV melanoma	10/9/2014	Bristol-Myers Squibb Company
10/16/2015	Idarucizumab	Praxbind	To reverse the anticoagulant effect of dabigatran due to uncontrolled life-threatening bleeding	5/28/2015	Boehringer Inhelheim Pharmaceuticals, Inc.
10/20/2015	Human factor X	Coagadex	Treatment of hereditary factor X deficienct	11/8/2007	Bio Products Laboratory

Marketing Approval	Generic Name	Trade Name	Designation (may be abbreviated)	Orphan Designation	Company
10/22/2015	Liposomal irinotecan	Onivyde	Treatment of pancreatic cancer	10/22/2015	Ipsen Bioscience, Inc.
10/23/2015	Asfotase alfa	Strensiq	Treatment of hypophosphatasia	9/12/2008	Alexion Pharmaceuticals, Inc.
10/23/2015	Trabectedin	Yondelis	Treatment of soft tissue sarcoma	9/30/2004	Janssen Research & Development, LLC
10/27/2015	Talimogene laherparepvec	Imlygic	Treatment of stage IIb-stage IV melanoma	3/14/2011	BioVex, Inc.
10/28/2015	Ipilimumab	Yervoy	Treatment of high risk Stage II, Stage III, and Stage IV melanoma	6/3/2011	Bristol-Myers Squibb Company
11/10/2015	Cobimetinib	Cotellic	Treatment of stage IIB, IIC, III, and IV melanoma with BRAFV600 mutation	1/31/2014	Genentech, Inc.
11/13/2015	Osimertinib	Tagrisso	Treatment of epidermal growth factor receptor mutation-positive non-small cell lung cancer	9/4/2014	AstraZeneca Pharmaceuticals LP
11/20/2013	Pegfilgratism	Neulasta	Treatment of subjects at risk of developing myelosuppression after a radiological or nuclear incident	11/20/2013	Amgen, Inc.
11/16/2015	Daratumumab	Darzalex	Treatment of multiple myeloma	5/6/2013	Janssen Biotech, Inc.
11/20/2015	Ixazomib citrate	Ninlaro	Treatment of multiple myeloma	2/18/2011	Millenium Pharmaceuticals
11/23/2015	Anthrax vaccine adsorbed	Biothrax	For post-exposure prophylaxis of anthrax disease resulting from suspected or confirmed Bacillus anthracis exposure	4/11/2014	Emergent BioDefense Operations Lansing LLC
11/24/2015	Necitumumab	Portrazza	Treatment of squamous non-small cell lung cancer	11/20/2015	Eli Lilly and Company
11/30/2015	Elotuzumab	Empliciti	Treatment of multiple myeloma	9/1/2011	Bristol-Myers Squibb Company
12/7/2015	Bendamustine	Bendeka	Treatment of chronic lymphocytic leukemia	7/2/2014	Eagle Pharmaceuticals, Inc.
12/8/2015	Recombinant von Willebrand factor	Vonvendi	Treatment of von Willebrand disease	11/23/2010	Baxalta US, Inc.
12/8/2015	Sebelipase alfa	Kanuma	Treatment of lysosomal acid lipase deficiency	7/1/2010	Alexion Pharmaceuticals, Inc.
12/11/2015	Uridine triacetate	Vistogard	An antidote in the treatment of 5-fluorouracil or capecitabine poisoning	5/1/2009	Wellstat Therapeutics, Inc.

Marketing Approval	Generic Name	Trade Name	Designation (may be abbreviated)	Orphan Designation	Company
12/11/2015	Alectinib	Alecensa	Treatment of ALK-positive non-small cell lung cancer	1/27/2015	Genentech, Inc.
12/18/2015	Pembrolizumab	Keytruda	Treatment of Stage IIB through IV malignant melanoma	11/19/2012	Merck, Sharpe & Dohme Corporation
12/21/2015	Selexipag	Uptravi	Treatment of pulmonary arterial hypertension	4/30/2010	Actelion Ltd
1/19/2016	Ofatumumab	Arzerra	Treatment of chronic lymphocytic leukemia	3/10/2009	Novartis Pharmaceuticals Corporation
1/28/2016	Eribulin Mesylate	Halaven	Treatment of soft tissue sarcoma	5/14/2012	Eisai, Inc.
1/29/2016	Acetylylcysteine effervescent tablets	Cetylev	Preventing hepatic injury from acetaminophin overdose	2/24/2015	Arbor Pharmaceuticals, Inc.
2/26/2016	Obinutuzumab	Gazyva	Treatment of follicular lymphoma	4/15/2015	Genentech, Inc.
2/26/2016	Everolimus	Afinitor	Treatment of neuroendocrine tumors	2/14/2008	Novartis Pharmaceuticals Corporation
3/4/2016	Recombinant fusion protein linking coagulation factor IX with albumin	Idelvion	Treatment of patients with congenital factor IX deficiency (hemophilia B)	4/27/2012	CSL Behring, LLC
3/4/2016	Ibrutinib	Imbruvica	Treatment of chronic lymphocytic leukemia	4/6/2012	Pharmacylics, LLC
3/10/2016	Melphalan	Evomela	High dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation	11/24/2008	Spectrum Pharmaceuticals, Inc.
3/18/2016	Obiltoxaximab	Anthim	Treatment of exposure to B. anthracis spores	6/9/2006	Elusys Therapeutics, Inc.
3/30/2016	Defibrotide	Defitelio	For the treatment of hepatic veno-occlusive disease	5/21/2003	Jazz Pharmaceuticals, Inc.
4/8/2016	Methylene blue	Provayblue	Treatment of hereditary and acquired methemoglobinemia	12/18/2012	Provepharm SAS
4/11/2016	Venetoclax	Venclexta	Treatment of chronic lymphocytic leukemia	9/20/2012	AbbVie, Inc.
4/15/2016	Riboflavin ophthalmic solution & ultraviolet A	Photrexa viscous	Treatment of keratoconus	9/2/2011	Avedro, Inc.
4/15/2016	Afatinib	Gilotrif(R)	Treatment of non-small cell lung cancer with squamous histology	8/3/2015	Boehringer Ingelheim Pharmaceuticals, Inc.
4/22/2016	Nitisinone	Orfadin	Treatment of tyrosinemia type 1	5/16/1995	Swedish Orphan Biovitrum AB
5/6/2016	Ibrutinib	Imbruvica	Treatment of small lymphocytic lymphoma	5/30/2013	Pharmacylics, LLC

Marketing Approval	Generic Name	Trade Name	Designation (may be abbreviated)	Orphan Designation	Company
5/17/2016	Nivolumab	Opdivo	Treatment of Hodgkin lymphoma	8/7/2014	Bristol-Myers Squibb Company
5/27/2016	Obeticholic acid	Ocaliva	Treatment of primary biliary cirrhosis	4/9/2008	Interept Pharmaceuticals, Inc.
5/27/2016	Rosuvastatin	Crestor	For the treatment of pediatric homozygous familial hypercholesterolemia	2/4/2014	iPR Pharmaceuticals, Inc.
6/1/2016	Gallium Ga 68 dotatate	Netspot	Diagnostic for the clinical management of neuroendocrine tumors	12/31/2013	Advanced Accelerator Applications
6/30/2016	Adalimumab	Humira	Treatment of non-infectious intermediate, posterior, or pan-uveitis, or chronic non-infectious anterior uveitis	5/13/2014	AbbVie, Inc.
7/15/2016	Riboflavin ophthatlmic solution & ultraviolet A	Photrexa viscous	Treatment of corneal ectasia following refractive surgery	12/2/2011	Avedro, Inc.
7/29/2016	Botulinum toxin type A	Dysport	Treatment of dynamic muscle contractures in pediatric cerebral palsy patients	10/20/1999	Ipsen Limited
8/30/2016	Ofatumumab	Arzerra	Treatment of chronic lymphocytic leukemia	3/10/2009	Novartis Pharmaceuticals Corporation
9/19/2016	Eteplirsen	Exondys 51	Treatment of Duchenne Muscular Dystrophy	10/23/2007	Sarepta Therapeutics, Inc.
9/23/2016	Canakinumab	Illaris	Treatment of familial mediterranean fever	12/5/2013	Novartis Pharmaceuticals Corporation
9/23/2016	Canakinumab	Illaris	Treatment of hyperimmunoglobulinemia D and periodic fever syndrome	12/5/2013	Novartis Pharmaceuticals Corporation
9/23/2016	Canakinumab	Illaris	Treatment of TNF-receptor associated periodic syndrome (TRAPS)	9/4/2012	Novartis Pharmaceuticals Corporation
9/28/2016	Lumacaftor	Orkambi	Treatment of cystic fibrosis	6/30/2014	Vertex Pharmaceuticals, Inc.
10/07/2016	Intravenous carbamazepine	Carnexiv	Treatment of epilepsy patients who cannot take anything by mouth (NPO)	6/27/2013	Lundbeck LLC
10/18/2016	Paricalcitol	Zemplar	Treatment of pediatric hyperparathyroidism	10/27/2015	AbbVie, Inc.
10/19/2016	Mebendazole	Vermox	Treatment of single or mixed gastrointestinal infestations	9/3/2014	Janssen Pharmaceutical Research & Development, LLC
10/19/2016	Olaratumab	Lartruvo	Treatment of soft tissue sarcoma	10/9/2014	Eli Lilly and Company

Marketing Approval	Generic Name	Trade Name	Designation (may be abbreviated)	Orphan Designation	Company
11/21/2016	Daratumumab	Darzalex	Treatment of multiple myeloma	5/6/2013	Janssen Biotech, Inc.
12/6/2016	Bevacizumab	Avastin	Therapeutic treatment of patients with ovarian cancer	2/9/2006	Genentech, Inc.
12/6/2016	Bevacizumab	Avastin	Treatment of primary peritoneal carcinoma	11/2/2010	Genentech, Inc.
12/6/2016	Bevacizumab	Avastin	Treatment of fallopian tube carcinoma	11/23/2010	Genentech, Inc.
12/19/2016	Rucaparib	Rubraca	Treatment of ovarian cancer	7/31/2012	Clovis Oncology, Inc.
12/23/2016	Nusinersen	Spinraza	Treatment of spinal muscular atrophy	4/18/2011	Biogen, Inc.
1/18/2017	Imbrutinib	Imbruvica	Treatment of patients with extranodal marginal zone lymphoma (mucosa associated lymphoid tissue [MALT type] lymphoma)	2/2/2016	Pharmacylics, LLC
1/18/2017	Imbrutinib	Imbruvica	Treatment of splenic marginal zone lymphoma	2/5/2015	Pharmacylics, LLC
1/18/2017	Imbrutinib	Imbruvica	Treatment of nodal marginal zone lymphoma	2/5/2015	Pharmacylics, LLC
1/26/2017	Thiotepa	Tepadina	Conditioning treatment prior to hematopoietic stem cell transplantation	4/2/2007	Adienne S.A.
2/9/2017	Deflazacort	Emflaza	Treatment of Duchenne muscular dystrophy	8/16/2013	PTC Therapeutics, Inc.
2/22/2017	Lenalidomide	Revlimid	Treatment of multiple myeloma	9/20/2001	Celgene Corporation
2/28/2017	Telotristat etiprate	Xermelo	Treatment of carcinoid syndrome in patients with neuroendocrine tumors	3/19/2012	Lexicon Pharmaceuticals, Inc.
3/14/2017	Pembrolizumab	Keytruda	Treatment of Hodgkin lymphoma	12/30/2015	Merck, Sharp & Dohme Corporation
3/23/2017	Avelumab	Bavencio	Treatment of merkel cell carcinoma	9/21/2015	EMD Serono Research and Development Institute, Inc.
3/27/2017	Niraparib	Zejula	Treatment of ovarian cancer	4/30/2010	TESARO, Inc.
4/3/2017	deutetrabenazine	Austedo	Treatment of Huntington's Disease	11/5/2014	Teva Pharmaceutical, Inc.
4/7/2017	Ledipasvir	Harvoni	Treatment of chronic hepatitis C virus (HCV) infection in pediatric patients	10/12/2016	Gilead Sciences, Inc.
4/7/2017	Sofosbuvir	Sovaldi	Treatment of pediatric chronic hepatitis C virus infection	10/25/2016	Gilead Sciences, Inc.
4/25/2017	Methotrexate oral solution	Xatmep	Treatment of oligoarticular juvenile idiopathic arthritis and polyarticular juvenile idiopathic arthritis in children	8/27/2015	Silvergate Pharmaceuticals, Inc.

Marketing Approval	Generic Name	Trade Name	Designation (may be abbreviated)	Orphan Designation	Company
4/25/2017	Nivolumab	Opdivo	Treatment of Hodgkin lymphoma	8/7/2014	Bristol-Myers Squibb Company
4/25/2017	Methotrexate oral solution	Xatmep	Treatment of acute lymphoblastic leukemia in pediatric patients	5/28/2015	Silvergate Pharmaceuticals, Inc.
4/27/2017	Regorafenib	Stivarga	Treatment of hepatocellular carcinoma	6/4/2015	Bayer HealthCare Pharmaceuticals, Inc.
4/27/2017	Cerliponase alfa	Brineura	Treatment of neuronal ceroid lipofuscinosis type 2	4/1/2013	BioMarin Pharmaceutical, Inc.
4/30/2017	Midostaurin	Rydapt	Treatment of mastocytosis	4/30/2017	Novartis Pharmaceuticals Corporation
4/28/2017	Glycerol phenylbutyrate	Ravicti	Maintenance treatment of patients with deficiencies in enzymes of the urea cycle	4/27/2009	Horizon Pharma USA, Inc.
4/28/2017	Brigatinib	Alunbrig	Treatment of anaplastic lymphoma kinase-positive (ALK+), c-ros 1 oncogene positive (ROS1+), or epidermal growth factor receptor positive (EGFR+) non-small cell lung cancer (NSCLC)	4/28/2016	ARIAD Pharmaceuticals, Inc.
4/28/2017	Midostaurin	Rydapt	Treatment of acute myeloid leukemia	7/7/2009	Novartis Pharmaceuticals Corporation
5/1/2017	Sterile talc	Steritalc	Treatment of malignant pleural effusion	12/8/1997	Novatech SA
5/1/2017	Sterile talc	Steritalc	Treatment of pneumothorax	12/8/1997	Novatech SA
5/5/2017	Edaravone	Radicava	Treatment of amyotrophic lateral sclerosis (ALS)	5/12/2015	Mitsubishi Tanabe Pharma Corporation
5/18/2017	Deferasirox	Exjade	Treatment of chronic iron overload in patients with transfusion-dependent anemias	11/21/2002	Novartis Pharmaceuticals Corporation
5/18/2017	Deferasirox	Exjade	Treatment of chronic iron overload in alpha-thalassemia	2/24/2015	Novartis Pharmaceuticals Corporation
5/26/2017	Ceritinib	Zykadia	Treatment of patients with non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase(ALK)-positive	9/27/2013	Novartis Pharmaceuticals Corporation
6/6/2017	5-aminolevulinic acid	Gleolan	Visualization of malignant tissue during surgery for malignant glioma (WHO grades III and IV)	1/15/2013	NX Development Corporation
6/16/2017	Daratumumab	Darzalex	Treatment of multiple myeloma	5/6/2013	Janssen Biotech, Inc.

Marketing Approval	Generic Name	Trade Name	Designation (may be abbreviated)	Orphan Designation	Company
6/22/2017	C1-esterase-inhibitor	Haegarda	Prevention and/or treatment of acute attacks of hereditary angioedema	10/16/1992	CSL Behring LLC
6/22/2017	Dabrafenib	Tafinler	Treatment of patients with BRAF mutation positive non-small cell lung cancer	10/20/2014	Novartis Pharmaceuticals Corporation
6/22/2017	Rituximab and recombinant human hyaluronidase	Rituxan Sc	Treatment of follicular lymphoma	8/22/2016	Genentech, Inc.
6/22/2017	Rituximab and recombinant human hyaluronidase	Rituxan Sc	Treatment of diffuse large B-cell lymphoma	9/7/2016	Genentech, 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) (2016)	Population Growth (2016)	GDP (PPP) (2016)	GDP Real Growth Rate (2016)	Per capita GDP (PPP) (2016)	Life Expectancy (Years) (2016)
China	1,373	0.43%	$21.1 trillion	6.7%	$14,600	76
Hong Kong	7	0.35%	$427.4 billion	1.4%	$58,100	83
India	1,266	1.19%	$8.7 trillion	7.6%	$6,700	69
Indonesia	258	0.89%	$3.0 trillion	5.0%	$11,700	73
Japan	127	-0.19%	$4.9 trillion	0.5%	$38,900	85
Korea	51	0.18%	$1.9 trillion	0.5%	$37,900	82
Malaysia	31	1.40%	$863 billion	4.2%	$27,200	75
Philippines	103	1.59%	$807 billion	6.9%	$7,700	69
Singapore	6	1.86%	$488 billion	2%	$87,100	85
Taiwan	23	0.20%	$1.1 trillion	1.5%	$49,500	80
Thailand	68	0.32%	$1.2 trillion	3.2%	$16,800	75
Vietnam	95	0.95%	$595 billion	6.1%	$6,400	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 around $200 billion (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 (2017)

Country	Pharmaceutical Market Size (US$)
China	$107 billion
Hong Kong	$1.8 billion
India	$24 billion
Indonesia	$6.5 billion
Japan	$104.5 billion
Korea	$19 billion
Malaysia	$3.1 billion
Philippines	$3.8 billion
Singapore	$948 million
Taiwan	$6.9 billion
Thailand	$6.3 billion
Vietnam	$5.1 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 4.4 billion, making up close to two-thirds of the world's 7.5 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 figure is less than the $3.3 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 unprofitable, drugs. As of December 2016, the MHLW had designated 336 products as orphan drugs. Of these, 276 have been approved for marketing (see Table 4 below).

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. If the drug is used to treat a "designated intractable disease" (*nanbyou*), the number of patients affected by the disease can be as large as 180,000 people.

3. 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).

4. 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, Health, and Nutrition (NIBIOHN), which is part of the Japanese equivalent of the US's National Institutes of Health (NIH). NIBIOHN 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: 1 official, 2 duplicate	a. Product name b. Ingredients c. Manufacturing process d. Dosage and administration e. Possible side-effects f. Supporting data as a life-saving drug g. Company name and address h. Marketing Authorization Holder information 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. b. Proposed indication(s). c. Reasons why the drug (therapy) is needed. d. List of similar products/treatments available in Japan. 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. b. Estimated cost of clinical trials. c. Number of patients needed for the trials. 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. b. US FDA NDA approval number and date. c. EU product summary and basis of approval. d. EMEA registration number and date. e. Any clinical data for Asian patients. f. Any marketing information in foreign countries. 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 First choice: Second choice: 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 NIBIOHN 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, NIBIOHN 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 NIBIOHN 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 July, 2017*
** 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 NIBIOHN 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 NIBIOHN form. A sample of this form is provided in section 5.4.8.2 below.

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 NIBIOHN 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 NIBIOHN 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 NIBIOHN 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?

NIBIOHN provides detailed guidelines on the financial aid application process for orphan drug applicants.

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 NIBIOHN. Pharmaceutical companies should provide a project/research update to NIBIOHN on a regular basis and notify NIBIOHN of any project delays or substantive changes to the development plan or situation. In the case of a delay (or project cancellation), NIBIOHN 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/

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, Health, and Nutrition
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@nibiohn.go.jp
Website: http://www.nibiohn.go.jp/en/activities/orphan-support.html

5.6 ORPHAN DRUG ASSOCIATIONS

The Japan Society of Human Genetics
Address: 5-1 Kojimachi, Chiyoda-ku, Tokyo, Japan 102-8481
Phone: +81-3-5216-5423
Fax: +81-3-5216-5552
Email: info-jshg@congre.co.jp
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: 3-25-8 Nishishimbashi, Minato-ku, Tokyo, Japan 105-0003
Phone: +81-96-373-5191
Fax: +81-96-366-3471
Email: jsimd@jikei.ac.jp
Website: http://jsimd.net/

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 July 13, 2017

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 preparation containing the cells of Streptococcus pyogenes treated with benzylpenicillin 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 immunoglobuline, 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.
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.
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.

Date Approved	Generic Name	Trade Name	Approved Indication	Date Designated	Company
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.
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.
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	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.

Date Approved	Generic Name	Trade Name	Approved Indication	Date Designated	Company
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.
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.

Date Approved	Generic Name	Trade Name	Approved Indication	Date Designated	Company
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.
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.

Date Approved	Generic Name	Trade Name	Approved Indication	Date Designated	Company
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.
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: · Moderate to severe active stage · 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.

Date Approved	Generic Name	Trade Name	Approved Indication	Date Designated	Company
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; 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.
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.
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.

Date Approved	Generic Name	Trade Name	Approved Indication	Date Designated	Company
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.
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.

Date Approved	Generic Name	Trade Name	Approved Indication	Date Designated	Company
1/4/2007	Doxorubicin HCl Liposome	Doxil injection 20mg	AIDS-related Kaposi's sarcoma	5/8/2006	Janssen Pharmaceutical 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 Co.
4/18/2007	Alglucosidase alfa	Myozyme drip injection 50mg	Glycogen storage disease type II	2/10/2006	Genzyme Japan K.K.
10/4/2007	Idursulfase	Elaprase drip infusion 6mg	Mucopolysaccharidosis Type II	12/14/2006	Genzyme Japan 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 K.K.
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 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) 2. Confirmation of the accumulation site of ibritumomab tiuxetan（recombinant）	1/13/2005	Bayer Holding Ltd.

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1/25/2008	Tacrolimus hydrate	Talimus eyedrops 0.1%	Vernal keratoconjunctivitis	7/7/2004 12/13/2005	Astellas Pharmaceutical Inc. 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.
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 Acute graft-versus-host disease (GVHD) after hematopoietic stem cell transplantation	11/15/1993 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 Benet tablet 17.5 mg	Paget's disease of bone	6/9/2006	Ajinomoto Co. Inc. Takeda Pharmaceutical Co., Ltd.

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7/16/2008	Argatroban	Novastan HI injection 10 mg/2 mL 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 Daiichi-Sankyo Company, Ltd.
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.
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.

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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 BeneFIX IV injection 1000 IU 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.
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 Prograf capsule 1 mg Prograf granule 0.2 mg 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 Kenketsu Venilon-I for IV injection 1000 mg Kenketsu Venilon-I for IV injection 2500 mg 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

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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 Ltd.
10/27/2010	Precipitated H5N1 influenza vaccine	H5N1 precipitated influenza vaccine “Kaketsuken”	Prophylaxis of H5N1 influenza	6/9/2006	Kaketsuken
1/21/2011	Azacitidine	Vidaza for injection 100 mg	Myelodysplastic syndrome	11/17/2008	Nippon Shinyaku Co., Ltd.
5/20/2011	Argatroban	Novastan HI injection 10 mg/2 mL 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 Daiichi-Sankyo Company, Ltd.
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: · Moderate to severe active stage · 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.

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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 Venoglobulin IH 5% IV injection 1 g/20 mL Venoglobulin IH 5% IV injection 2.5 g/50 mL 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 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 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 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.

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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 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	Stiripentol	Diacomit dry syrup 250 mg Diacomit dry syrup 500 mg 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.
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 Afinitor tablet 5 mg	Renal angiomyolipoma associated with tuberous sclerosis (only for tablet preparations) Subependymal giant cell astrocytoma associated with tuberous sclerosis	12/14/2011	Novartis Pharma K.K.
12/25/2012	Everolimus	Afinitor dispersible tablet 2 mg Afinitor dispersible tablet 3 mg	Renal angiomyolipoma associated with tuberous sclerosis (only for tablet preparations) Subependymal giant cell astrocytoma associated with tuberous sclerosis	12/14/2011	Novartis Pharma K.K.

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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 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	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	Precipitated H5N1 influenza vaccine	H5N1 precipitated influenza vaccine "SEIKEN”1 mL	Prophylaxis of H5N1 influenza	6/9/2006	Denka Seiken Co., Ltd.
4/26/2013	Cell culture-derived whole virion prototype vaccine	Cell culture influenza vaccine (prototype vaccine) "Baxter" 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 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 Prograf capsule 1 mg	Interstitial pneumonia associated with polymyositis or dermatomyositis	9/13/2012	Astellas Pharma Inc.

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6/18/2013	BLB-750 (H5N1 cell culture influenza vaccine)	H5N1 cell culture influenza vaccine "Baxter" H5N1 cell culture influenza vaccine "Takeda"	Prophylaxis of H5N1 influenza	6/16/2010 6/10/2011	Baxter Takeda Pharmaceutical Co., Ltd.
9/20/2013	Tafamidis meglumine	Vyndaqel Capsules 20 mg	Peripheral neurologic impairment in transthyretin familial amyloid polyneuropathy	12/14/2011	Pfizer Japan Inc.
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 Adempas tablet 1.0mg 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 Regpara Tablet 75mg	Hypercalcemia associated with parathyroid carcinoma or unresectable/postoperative recurrence primary hyperparathyroidism	2/11/2012	Kyowa Hakko Kirin Co., Ltd.
3/17/2014	Mogamulizumab	Poteligeo Injection 20 mg	Relapsed or refractory CCR4-positive peripheral T-cell lymphoma and relapsed or refractory CCR4-positive cutaneous T-cell lymphoma	8/11/2010	Kyowa Hakko Kirin Co., Ltd.
3/24/2014	Tolvaptan	Samsca Tablets 7.5 mg Samsca Tablets 15 mg Samsca Tablets 30 mg	Autosomal dominant polycystic kidney disease in patients whose kidney volume already have increased and enlarged at a rapid rate	8/11/2006	Otsuka Pharmaceutical Co., Ltd.
3/24/2014	Natalizumab	Tysabri for I.V. Infusion 300 mg	Prevention of relapse and for delaying the accumulation of physical disability in multiple sclerosis	5/20/2008	Biogen Idec Japan Ltd.
3/24/2014	Anhydrous caffeine	Respia Injection or oral solution 60 mg	Primary apnea (apnea of prematurity) in immature or low birth weight infants	8/8/2011	Nobelpharma Co., Ltd.
3/24/2014	Dolutegravir sodium	Tivicay Tablets 50 mg	HIV infection	9/13/2013	ViiV Healthcare K.K.

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3/24/2014	Cell culture-derived influenza emulsion HA vaccine (H5N1)	Cell Culture-derived Influenza Emulsion HA Vaccine H5N1 for Intramuscular Injection "Kaketsuken"	Prophylaxis of pandemic influenza (H5N1)	6/13/2012	Kaketsuken [The Chemo-Sero-Therapeutic Research Institute]
3/24/2014	Adsorbed cell culturederived influenza vaccine (H5N1)	Adsorbed Cell Culture-derived Influenza Vaccine H5N1 for Intramuscular Injection 30μg/mL and 60μg/mL	Prophylaxis of pandemic influenza (H5N1)	12/11/2012	Kitasato Daiichi Sankyo Vaccine Co., Ltd.
5/23/2014	Interferon gamma-1a	Imunomax-γ for Injection 50 Imunomax-γ for Injection 100	Mycosis fungoides and Sézary syndrome	5/11/2012	Shionogi & Co., Ltd.
5/23/2014	Denosumab	Ranmark Subcutaneous Injection 120 mg	Giant cell tumor of bone	6/17/2013	Daiichi Sankyo Company, Limited
6/20/2014	Sorafenib tosylate	Nexavar Tablets 200 mg	Unresectable differentiated thyroid carcinoma	9/13/2013	Bayer Yakuhin, Ltd.
7/4/2014	Alectinib hydrochloride	Alecensa Capsule 20 mg Alecensa Capsule 40 mg	Unresectable advanced/relapsed ALK fusion gene-positive non-small-cell lung cancer	9/13/2013	Chugai Pharmaceutical Co., Ltd.
7/4/2014	Ruxolitinib phosphate	Jakavi Tablets 5 mg	Myelofibrosis	9/8/2011	Novartis Pharma K.K.
7/4/2014	Cysteamine bitartrate	Nicystagon Capsules 50 mg Nicystagon Capsules 150 mg	Nephropathic cystinosis	5/11/2012	Mylan Seiyaku Ltd.
7/4/2014	Freeze-dried polyethylene glycol treated human normal immunoglobulin	kenketu Glovenin-I for I.V. Injection 2500 mg kenketu Glovenin-I for I.V. Injection 500 mg kenketu Glovenin-I for I.V. Injection 5000 mg	Stevens-Johnson syndrome and toxic epidermal necrolysis (for use when steroid drugs are not sufficiently effective)	11/14/2012	Nihon Pharmaceutical Co., Ltd.
7/4/2014	Sirolimus	Rapalimus Tablets 1 mg	Lymphangioleiomyomatosis	9/13/2012	Nobelpharma Co., Ltd.

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7/4/2014	Delamanid	Deltyba Tablets 50 mg	Multidrug-resistant pulmonary tuberculosis caused by delamanid-sensitive Mycobacterium tuberculosis	2/18/2008	Otsuka Pharmaceutical Co., Ltd.
8/29/2014	Rituximab	Rituxan Injection 10 mg/mL	Refractory nephrotic syndrome (for use in patients with frequent recurrence or steroid-dependent)	9/13/2012	Zenyaku Kogyo Co., Ltd.
9/26/2014	Alemtuzumab	MabCampath Intravenous infusion 30 mg	Relapsed or refractory chronic lymphocytic leukemia	8/16/2012	Sanofi K.K.
9/26/2014	Bosutinib hydrate	Bosulif Tablets 100 mg	Chronic myelogenous leukemia with resistance or intolerance to prior drug therapies	12/4/2013	Pfizer Japan Inc.
9/26/2014	Streptozocin	Zanosar for Intravenous Injection 1 g	Neuroendocrine tumors of the pancreas and gastrointestinal tract	11/16/2011	Nobelpharma Co., Ltd.
11/18/2014	Rilpivirine hydrochloride, Emtricitabine, Tenofovir disoproxil fumarate	Complera Combination Tablets	HIV-1 infection	--	Janssen Pharmaceutical K.K.
12/18/2014	Darbepoetin alfa	Nesp Injection	Anemia due to myelodysplastic syndrome	3/17/2014	Kyowa Hakko Kirin Co., Ltd.
12/26/2014	Vemurafenib	Zelboraf Tablet 240 mg	Unresectable malignant melanoma with BRAF mutation	9/13/2012	Chugai Pharmaceutical Co., Ltd.
12/26/2014	Elosulfase alfa	Vimizim Intravenous Infusion 5 mg	Mucopolysaccharidosis type IVA	12/11/2012	BioMarin Pharmaceutical Japan K.K.
3/16/2015	Dolutegravir sodium, Abacavir sulfate, Lamivudine	Triumeq Combination Tablets	HIV infection	9/13/2013	ViiV Healthcare K.K
3/26/2015	Cell culture-derived influenza emulsion HA vaccines	Cell Culture-derived Influenza Emulsion HA Vaccine (prototype) for Intramuscular Injection “Kaketsuken”	Prophylaxis of pandemic influenza	6/13/2012	Kaketsuken [The Chemo-Sero-Therapeutic Research Institute]

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3/26/2015	Lenvatinib mesilate	Lenvima Capsule 4 mg Lenvima Capsule 10 mg	Unresectable thyroid cancer	8/16/2012	Eisai Co., Ltd.
3/26/2015	Pomalidomide	Pomalyst Capsules 1 mg Pomalyst Capsules 2 mg Pomalyst Capsules 3 mg Pomalyst Capsules 4 mg	Relapsed or refractory multiple myeloma	6/11/2014	Celgene K.K.
3/26/2015	Catridecacog	NovoThirteen IV injection 2500	Control of bleeding tendency in patients with congenital blood coagulation factor XIII A-subunit deficiency	5/13/2014	Novo Nordisk Pharma Ltd.
3/26/2015	Colistin sodium methanesulfonate	Aldreb for Injection 150 mg	Infections caused by colistinsensitive Escherichia coli, Citrobacter, Klebsiella, Enterobacter, Pseudomonas aeruginosa, and Acinetobacter (limited to the strains resistant to other antimicrobial drugs)	11/10/2010	GlaxoSmithKline K.K.
3/26/2015	Eliglustat tartrate	Cerdelga Capsule 100 mg	Various symptoms of Gaucher disease (anemia, thrombocytopenia, hepatosplenomegaly, and bone disease)	3/9/2011	Genzyme Japan K.K.
5/26/2015	Talaporfin sodium	Laserphyrin 100 mg for Injection	Recurrent esophageal cancer associated with local persistence	3/17/2014	Meiji Seika Pharma Co., Ltd.
5/26/2015	Peginterferon alfa-2b	Pegintron Powder for Injection	Adjuvant treatment of melanoma	9/17/2014	MSD K.K.
5/26/2015	Rituximab	Rituxan Injection 10 mg/mL	CD20-positive, B-cell non-Hodgkin's lymphoma	11/12/1998	Zenyaku Kogyo Co., Ltd.
6/26/2015	Edaravone	4 Radicut Inj. 30 mg Radicut Bag for I.V. Infusion 30 mg	Amyotrophic lateral sclerosis (ALS)	6/20/2005	Mitsubishi Tanabe Pharma Corporation
6/26/2015	Bortezomib	Velcade Injection 3 mg	Mantle cell lymphoma	11/10/2010	Janssen Pharmaceutical K.K.
7/3/2015	Nintedanib ethanesulfonate	Ofev Capsules 100 mg Ofev Capsules 150 mg	Idiopathic pulmonary fibrosis	9/18/2011	Nippon Boehringer Ingelheim Co., Ltd.

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7/3/2015	Asfotase alfa	Strensiq Subcutaneous Injection	Hypophosphatasia	8/21/2014	Alexion Pharma G.K.
7/3/2015	Ipilimumab	Yervoy Injection 50 mg	Unresectable melanoma	3/15/2013	Bristol-Myers K.K.
7/3/2015	Panobinostat lactate	Farydak Capsules 10 mg Farydak Capsules 15 mg	Relapsed or refractory multiple myeloma	9/17/2014	Novartis Pharma K.K.
8/24/2015	Bosentan hydrate	Tracleer Tablets 62.5 mg	Digital ulcer in patients with systemic scleroderma	12/8/2014	Actelion Pharmaceuticals Japan Ltd.
8/24/2015	Nitric oxide	INOflo for Inhalation 800 ppm	Pulmonary hypertension in the perioperative period of cardiac surgery	11/20/2014	INO Therapeutics LLC
8/24/2015	Infliximab	Remicade for I.V. Infusion 100	Entero-Behcet's disease, neuro-Behcet's disease, and vasculoBehcet's disease	4/1/1996	Mitsubishi Tanabe Pharma Corporation
9/28/2015	Bosentan hydrate	Tracleer pediatric dispersible tablets 32 mg	Pulmonary arterial hypertension	1/31/2003	Actelion Pharmaceuticals Japan Ltd.
9/28/2015	Trabectedin	Yondelis I.V. infusion 0.25 mg Yondelis I.V. infusion 1 mg	Soft tissue sarcoma	6/10/2011	Taiho Pharmaceutical Co., Ltd.
12/21/2015	Infliximab	Remicade for I.V. Infusion 100	Acute-phase Kawasaki's disease	9/13/2012	Mitsubishi Tanabe Pharma Corporation
1/22/2016	Bexarotene	Targretin Capsules 75 mg	Cutaneous T-cell lymphoma	3/15/2013	Minophagen Pharmaceutical Co., Ltd.
2/29/2016	Eribulin mesylate	Halaven Injection 1 mg	Soft tissue sarcoma	6/11/2014	Eisai Co., Ltd.
2/29/2016	Sorafenib tosilate	Nexavar Tablets 200 mg	Unresectable thyroid cancer	9/13/2013	Bayer Yakuhin, Ltd.
2/29/2016	Nivolumab	Opdivo Intravenous Infusion 20 mg Opdivo Intravenous Infusion 100 mg	Unresectable melanoma	6/17/2013	Ono Pharmaceutical Co., Ltd.

Date Approved	Generic Name	Trade Name	Approved Indication	Date Designated	Company
3/18/2016	Adsorbed cell culturederived influenza vaccine (H5N1)	Adsorbed Cell Culture-derived Influenza Vaccine H5N1 for Intramuscular Injection 30μg/mL	Paraphylaxis of of pandemic influenza (H5N1)	12/11/2012	Kitasato Daiichi Sankyo Vaccine Co., Ltd.
3/28/2016	Vigabatrin	Sabril Granule Sachets 500 mg	Infantile spasms	9/17/2014	Sanofi K.K.
3/28/2016	Sebelipase alfa	Kanuma Intravenous Infusion 20 mg	Lysosomal acid lipase deficiency	8/16/2012	Alexion Pharma G.K.
3/29/2016	Rituximab	Rituxan Injection 10 mg/mL	Prophylaxis of antibody-mediated rejection in patients who underwent ABO incompatible kidney or liver transplantation	5/25/2015	Zenyaku Kogyo Co., Ltd.
5/23/2016	Bevacizumab	Avastin 100 mg/4 mL Intravenous Infusion Avastin 400 mg/16 mL Intravenous Infusion	Advanced or recurrent cervical cancer	9/14/2015	Chugai Pharmaceutical Co., Ltd.
6/17/2016	Elvitegravir/ Cobicistat/ Emtricitabine/ Tenofovir alafenamide fumarate	Genvoya Combination Tablets	HIV-1 infection	11/19/2015	Japan Tobacco Inc.
7/4/2016	Carfilzomib	Kyprolis for Intravenous Injection10 mg Kyprolis for Intravenous Injection 40 mg	Relapsed or refractory multiple myeloma	8/20/2015	Ono Pharmaceutical Co., Ltd.
7/4/2016	Propranolol hydrochloride	Hemangiol Syrup for Pediatric 0.375%	Infantile hemangioma	11/15/2013	Maruho Co., Ltd.
7/4/2016	Levodopa/ Carbidopa hydrate	Duodopa Enteral Combination Solution	Parkinson's disease	5/12/2009	AbbVie G.K.

Date Approved	Generic Name	Trade Name	Approved Indication	Date Designated	Company
8/26/2016	Bendamustine hydrochloride	Treakisym Injection 100 mg	Chronic lymphocytic leukemia	10/28/2009	SymBio Pharmaceuticals Limited
9/28/2016	Pembrolizumab	Keytruda Injection 20 mg Keytruda Injection 100 mg	Unresectable melanoma	9/17/2014	MSD K.K.
9/28/2016	Elotuzumab	Empliciti for I.V. Infusion 300 mg Empliciti for I.V. Infusion 400 mg	Relapsed or refractory multiple myeloma	11/19/2015	Bristol-Myers K.K.
9/28/2016	Rifaximin	Rifxima Tablets 200 mg	Hepatic encephalopathy	5/13/2013	Aska Pharmaceutical Co., Ltd
9/28/2016	Selexipag	Uptravi Tablets 0.2 mg Uptravi Tablets 0.4 mg	Pulmonary arterial hypertension	9/17/2014	Nippon Shinyaku Co., Ltd.
9/28/2016	Lomitapide mesilate	Juxtapid Capsules 5 mg Juxtapid Capsules 10 mg Juxtapid Capsules 20 mg	Homozygous familial hypercholesterolemia	9/3/2013	Aegerion Pharmaceuticals K.K.
9/28/2016	Ponatinib hydrochloride	Iclusig Tablets 15 mg	Chronic myelogenous leukemia and recurrent or refractory Philadelphia chromosomepositive acute lymphoblastic leukemia	9/14/2015	Otsuka Pharmaceutical Co., Ltd.
9/28/2016	Carglumic acid	Carbaglu Dispersible Tablets 200 mg	Hyperammonemia due to Nacetylglutamate synthetase deficiency, isovaleric acidemia, methylmalonic acidemia, and propionic acidemia	11/20/2014	Pola Pharma Inc.
9/28/2016	Bendamustine hydrochloride	Treakisym Injection 25 mg	Chronic lymphocytic leukemia	6/13/2012	SymBio Pharmaceuticals Limited
11/22/2016	Darunavir ethanolate/ Cobicistat	Prezcobix Combination Tablets	HIV infection	11/16/2014	Janssen Pharmaceutical K.K.
12/2/2016	Nivolumab	Opdivo Intravenous Infusion 20 mg Opdivo Intravenous Infusion 100 mg	Relapsed or refractory classical Hodgkin's lymphoma	3/16/2016	Ono Pharmaceutical Co., Ltd.

Date Approved	Generic Name	Trade Name	Approved Indication	Date Designated	Company
12/2/2016	Ibrutinib	Imbruvica Capsules 140 mg	Relapsed or refractory mantle cell lymphoma	6/11/2014	Janssen Pharmaceutical K.K.
12/9/2016	Emtricitabine/ Tenofovir alafenamide fumarate	Descovy Combination Tablets LT Descovy Combination Tablets HT	HIV-1 infection	11/19/2015	Japan Tobacco Inc.
12/19/2016	Plerixafor	Mozobil Injection 24 mg	Autologous peripheral blood stem cell transplantation	12/18/2015	Sanofi K.K.
12/19/2016	Dimethyl fumarate	Tecfidera Capsules 120 mg Tecfidera Capsules 240 mg	Accumulation of physical disability in multiple sclerosis	3/6/2007	Biogen Japan Ltd.
12/19/2016	Canakinumab	Ilaris for S.C. Injection 150 mg	Familial Mediterranean fever, TNF receptorassociated periodic syndrome, or hyper IgD syndrome	5/13/2014	Novartis Pharma K.K.
12/19/2016	Polyethylene glycol treated human normal immunoglobulin G	Kenketu Glovenin-I for I.V. Injection 2500 mg Kenketu Glovenin-I for I.V. Injection 500 mg Kenketu Glovenin-I for I.V. Injection 5000 mg	Motor disability due to chronic inflammatory demyelinating polyneuropathy	7/4/2014	Nihon Pharmaceutical Co., Ltd.

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

Note: Current to August 31, 2016

Date Designated	Generic Name	Expected Indication	Company
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.
10/13/2004	FTY-720	Renal transplantation.	Mitsubishi Tanabe Pharmaceutical Corp., Novartis Pharmaceutical K.K.
6/9/2006	Leuprorelin acetate	Spinobulbar muscular atrophy.	Takeda Pharmaceutical Co. Ltd.
6/6/2008	Forodesine hydrochloride	The following diseases when recurrent or intractable: ・Peripheral T-cell lymphoma ・Adult T-cell leukemia / lymphoma ・Cutaneous T-cell lymphoma ・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.
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 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.
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.

Date Designated	Generic Name	Expected Indication	Company
3/19/2012	Imatinib mesylate	Pulmonary arterial hypertension	Novartis Pharma K.K.
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	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	Miglustat Hydrochloride	Fabry's disease	GlaxoSmithKline K.K.
8/16/2012	Ecallantide	Acute attacks of hereditary angioedema	CMIC Holdings Co., Ltd.
8/16/2012	SBC-102	Lysosomal acid lipase deficiency	Synageva BioPharma Corp
9/13/2012	Bevacizumab (recombinant)	Glioblastoma	Chugai Pharmaceutical Co., Ltd
9/13/2012	Infliximab (recombinant)	Refractory Kawasaki disease	Mitsubishi Tanabe Pharma Corporation
11/14/2012	SAR302503	Myelofibrosis	Sanofi K.K.
12/11/2012	Precipitated influenza vaccine cell culture (prototype vaccine)	Prophylaxis for new strains of influenza	Kitasato Daiichi Sankyo Vaccine Co., Ltd.
5/13/2013	Aminolevulinic acid hydrochloride	Visualization of tumor tissue during surgical resection of non-muscle invasive bladder cancer	Nobelpharma Co., Ltd. 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	Ambrisentan	Chronic thromboembolic pulmonary hypertension	GlaxoSmithKline K.K.
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.
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	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.

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
2/26/2014	Dried sulfonated human immunoglobulin	Improvement of microscopic polyangiitis (limited to cases in which steroids are inadequate)	Kaketsuken, Teijin Pharma Limited
2/26/2014	Pralatrexate	Peripheral T- cell lymphoma	Mundipharma K.K.
3/17/2014	Talaporfin Sodium	Local failure after chemoradiotherapy or radiotherapy for esophageal cancer	Meiji Seika Pharma Co., Ltd
3/17/2014	Darbepoetin Alfa (Genetical Recombination)	Anemia with Myelodysplastic Syndromes	Kyowa Hakko Kirin Co., Ltd.
5/13/2014	EPI-743	Leigh syndrome	Dainippon Sumitomo Pharma Co., Ltd.
5/13/2014	Catridecacog	Inhibition of bleeding in patients with congenital factor XIII A-subunit deficiency	Novo Nordisk Pharma Ltd.
5/13/2014	Canakinumab (Genetical Recombination)	Mevalonate Kinase Deficiency	Novartis Pharma K.K.
5/13/2014	Canakinumab (Genetical Recombination)	TNF receptor-associated periodic syndrome	Novartis Pharma K.K.
5/13/2014	Canakinumab (Genetical Recombination	Familial Mediterranean fever	Novartis Pharma K.K.
6/11/2014	Icatibant	Acute attacks of hereditary angioedema	Shire Japan KK
6/11/2014	Ibrutinib	Chronic lymphocytic leukemia, small lymphocytic lymphoma, and Mantle cell lymphoma	Janssen Pharmaceutical K.K.
6/11/2014	Tocilizumab (genetical recombination)	Large Vessel Vasculitis	Chugai Pharmaceutical Co., Ltd
8/21/2014	Rituximab (recombinant)	Acquired thrombotic thrombocytopenic purpura	Zenyaku Kogyo Co., Ltd.
8/21/2014	ISIS 420915	Transthyretin Familial Amyloid Polyneuropathy	GlaxoSmithKline K.K.
8/21/2014	BG00012	Prevention of relapse and delay of physical disability progression in multiple sclerosis	Biogen Idec Japan Ltd.
9/17/2014	Selexipag	Pulmonary arterial hypertension	Nippon Shinyaku Co., Ltd

Date Designated	Generic Name	Expected Indication	Company
9/17/2014	MK-3475	Malignant melanoma	MSD K.K.
11/20/2014	Thalidomide	Crow-Fukase (POEMS) syndrome	Fujimoto Pharmaceutical Corporation
11/20/2014	Eculizumab (genetical recombination)	Prevention of NMO-IgG-positive relapsing neuromyelitis optica (NMO)	Alexion Pharma Godo Kaisha
11/20/2014	Isopropyl unoprostone	Retinitis pigmentosa	R-Tech Ueno, Ltd.
11/20/2014	Teduglutide (genetical recombination)	Short Bowel Syndrome	NPS Pharma K.K. and G.K
11/20/2014	Carglumic acid	Inhibition of rising blood levels of ammonia in the following associated diseases: N-acetylglutamate synthetase deficienc,Isovaleric academia,Methylmalonic academia and Propionic Acidemia	Pola Pharma INC.
12/8/2014	Eculizumab (genetical recombination)	Intractable myasthenia gravis	Alexion Pharma Godo Kaisha
5/25/2015	Metirosine	Improvement of catecholamine excess and various symptoms in pheochromocytoma	Ono Pharmaceutical Co., Ltd.
9/14/2015	Ponatinib Hydrochloride	Chronic myelogenous leukemia with resistance or intolerance to previous treatments and relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukemia	Otsuka Pharmaceutical Co., Ltd. -
9/14/2015	Bedaquiline Fumarate	Pulmonary multidrug-resistant tuberculosis (MDRTB)	Janssen Pharmaceutical K.K.
11/19/2015	Elotuzumab (Genetical Recombination)	Relapsed or refractory multiple myeloma	Bristol-Myers Squibb
12/18/2015	Sirolimus	Angiofibroma due to tuberous sclerosis complex	Nobelpharma Co., Ltd.
12/18/2015	Pyrimethamine	Toxoplasmosis	Glaxo SmithKline K.K.
12/18/2015	Sulfadiazine	Toxoplasmosis	Alcon Japan Ltd.
12/18/2015	Plerixafor	Mobilization of hematopoietic stem cells into peripheral blood for autologous peripheral blood stem cell transplantation in combination with G-CSF	Sanofi K.K.
12/18/2015	HBI-8000	Peripheral T- cell lymphoma	Huya Japan GK
2/25/2016	MK-8228	Cytomegalovirus antigenemia Cytomegalovirus infection and disease	MSD K.K.

Date Designated	Generic Name	Expected Indication	Company
2/25/2016	Ixazomib citrate	Relapsed or refractory multiple myeloma	Takeda Pharmaceutical Co., Ltd.
3/16/2016	Fampridine	Walk improvement of multiple sclerosis	Biogen Japan Ltd
3/16/2016	STM-279	Adenosin deaminase deficiency	Teijin Pharma Limited
3/16/2016	Tocilizumab (Genetical Recombination)	Systemic sclerosis	Chugai Pharmaceutical Co., Ltd. -
3/16/2016	Human alpha1-Proteinase Inhibitor	Severe alpha1-antitrypsin deficiency developed COPD	Grifols Japan K.K.
3/16/2016	Lyophilized Human Prothrombin Complex Concentrate	Rapid correction of international normalized ratio (INR) in patients receiving vitamin K antagonist therapy (e.g. warfarin) who experience acute major bleeding and/or who require a surgical or invasive medical procedure	CSL Behring K.K.
3/16/2016	Nivolmab (Geenetical Recombination)	Hodgkin's lymphoma	Ono Pharmaceutical Co., Ltd.
6/20/2016	Selexipag	Unresectable or postoperative residual/recurrence Chronic thromboembolic pulmonary hypertension	Nippon Shinyaku Co., Ltd
6/20/2016	Patisiran	Transthyretin Familial Amyloid Polyneuropathy	Genzyme Japan K.K.
6/20/2016	Lenalidomide Hydrate	Relapsed or refractory adult T-cell leukemia/lymphoma	Celgene K.K.
8/24/2016	Onoact	Life-threatening refractory and emergent cardiac arrhythmias: ventricular fibrillation and hemodaynamically unstable ventricular tachycardia	Ono Pharmaceutical Co., Ltd.
8/24/2016	Crizotinib	ROS1-fusion gene positive unresectable advanced and/or recurrent non-small cell lung cancer	Pfizer Japan Inc
8/24/2016	Romidepsin	Peripheral T-cell lymphoma	Celgene K.K.
8/24/2016	RO5534262	Prevention and reduction of bleeding episodes in patients with congenital FVIIl deficiency (hemophilia A)	Chugai Pharmaceutical Co., Ltd

6. TAIWAN

6.1 OVERVIEW

Taiwan's pharmaceutical market is valued at around $5.5 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 84 for women. By 2016, 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 diseases, certified by the Taiwan government. By 2016, the number had increased to more than 10,000. In 2017, the Taiwanese government officially categorized 209 diseases as "rare diseases".

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.

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	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.488, Sec. 6, Zhongxiao E. Road, Taipei, Taiwan 115
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/eng/

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 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 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 罕藥輸字第000012號 (62.5 mg) 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 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) 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(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(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) 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) 98年5月4日衛署藥字第0980305278號公告(solution for infusion)	94年5月23日 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 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 罕菌疫輸字第000001號 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 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 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 罕菌疫輸字第000007號 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 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 Niemann-Pick Disease Type C	94年1月28日衛署藥字第0940304588號公告(Type I Gaucher Disease) 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 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 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 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 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 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。 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 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 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) 95年1月26日罕藥製字第000010號(25 mg, 科進) 94年3月15日罕藥製字第000008號(25 mg, 吉帝) 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 吉帝藥品股份有限公司	

7. KOREA

7.1 OVERVIEW

The Korean pharmaceutical market is currently valued at around $19 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: Single dose toxicity Repeated dose toxicity Reproduction toxicity Genotoxicity 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: 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: 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 (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 $140 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，原產國家的衞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 : Tel. No. :
申請人營業地址 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 : ..... Signature : .....
日期 : 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?		
	(i). change of name, dosage form or active ingredient, please provide the original registration certificate of the existing product; or	☐	☐
	(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? 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 (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 almost 1.4 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, Chengdu, 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 was valued at about $108 billion in 2016 and is expected to continue to experience growth. China is the world's second largest drug market, and is expected to grow to $167 billion by 2020, representing an annual growth of 9.1%. 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. However, some Chinese drug companies are hoping to make new compounds. 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 three to six years to register. Moreover, the CFDA usually requires that a foreign company conduct clinical trials in China, even if the product has already been approved in a Western 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.

Drug registration fees for imported drugs are ¥376,000 for clinical trial approval and ¥593,900 for marketing approval. For generic drugs, applications are less costly with marketing approval with clinical testing costing about ¥318,000. There is currently no separate application process for orphan drugs; they follow the normal drug registration standards. However, this is subject to change in the near future as China formulates a comprehensive orphan drug policy.

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.

The National Reimbursement Drug List was recently updated in 2017 for the first time in 8 years, and 339 new drugs were added. The new list of 2,535 Western and traditional Chinese medicines includes drugs with US orphan designation such as gefitinib, a lung cancer drug sold as Iressa by AstraZeneca PLC.

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,” the Chinese Center for Disease Control and Prevenetion estimates that about 16.8 million Chinese patients have some type of rare disease. In May 2017, Chinese officials announced that they are compiling a draft list of rare diseases that may be released by the end of the year. Li Dingguo, chairman of the Shanghai Rare Disease Prevention and

Treatment Fund, said China's draft list covers more than 100 diseases. This list will serve as a basis for orphan drug policymaking.

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.

Many academic institutions and major hospitals have played an important role in the treatment of rare diseases. In August 2016, the Shanghai Institute of Materia Medica of the Chinese Academy of Sciences announced that their orphan drug program treating pulmonary arterial hypertension was approved by the CFDA to begin human clinical trials. Furthermore, researchers at Tongji Medical College in Wuhan and the FivePlus Molecular Medicine Institute in Beijing recently completed a clinical trial of gene therapy for Leber's hereditary optic neuropathy (LHON), a rare genetic disorder.

Domestic orphan drug development is extremely limited due to the lack of incentives. However, this is set to change as orphan drug legislation is implemented and there may also be a focus on rare diseases and conditions prevalent in the Chinese population such as certain sub-types of Fabry disease.

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. The only preferential treatment orphan drugs currently receive in China is priority review during registration. In May 2017, the China Food and Drug Administration (CFDA) published proposed groundbreaking orphan drug policies for public comment. The CFDA proposes that drugs and devices that treat designated rare diseases may apply for a clinical trial waiver. Orphan drugs and devices that have already been approved overseas may be granted a conditional approval without any domestic clinical studies. Follow-up studies as directed by the CFDA must be completed in China after conditional approval.

The CFDA currently 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

Chinese regulations do *not* specify a number of key materials, including how few patients a disease must have to be considered "rare." They *do* 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.

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: Jia-1, Fuxing Road, Haidian District, Beijing, P.R. China, 100038
Phone: +86-010-6858-5566
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 $4.3 billion. The US has a limited presence in the market, holding less than 8% of the market share; the UK, 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. However, this is quickly changing as the Philippines introduces new rare disease legislation.

On March 3, 2016, the Rare Diseases Act of the Philippines was signed into law, helping patients with rare diseases have better access to comprehensive healthcare. In the Rare Diseases Act, the Department of Health is charged with creating a Rare Disease Registry, and all patients with a rare disease are to be included in the registry. Furthermore, patients with rare diseases will be considered persons with disabilities, and enjoy privileges like priority programs and discounts. This classification allows for patients with rare diseases to qualify for discounts on healthcare services and medicines as specified in the Republic Act 9442.

As of January 2017, there were approximately 63 rare diseases officially registered, affecting 319 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.

Currently, only 28% of all newborns in the Philippines are screened for rare diseases, but this figure is soon set to improve as the Phillipine government makes rare disease detection a priority in its national rare disease strategy.

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 the Rare Diseases Act of the Philippines, the Department of Health was charged with creating a technical working group to determine what disorder or disease shall be considered a rare disease, and what the orphan drugs and products are. This working group is also responsible for formulating regulations on the approval and certification of orphan drugs.

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: callcenter@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 $3.7 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 31 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 Orphan Drugs in Malaysia

Malaysia is currently in the process of developing a national framework for rare disease management. As of July 2017, no specific regulations regarding rare diseases exist, but are expected in the near future.

Currently, government funding for the treatment of rare diseases is limited. The Malaysian government only subsidizes certain enzyme replacement therapies and treatments such as *alglucosidase alfa* and *elaprase*. Furthermore, this limited funding is only available to patients meeting selective criteria for eligibility and only at hospitals run by the Deparment of Health. However, Malaysia is one of few countries offering public funding for rare disease treatment.

Malaysia has a very high rate of newborn screening of rare diseases with more than 95% of newborns being screened.

13.5 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

13.6 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

Thailand has one of the more developed healthcare systems in Southeast Asia and the second largest pharmaceutical market, valued at $4.8 billion, second only to Indonesia. Furthermore, Thailand is a top destination for medical tourism, with many patients in neighboring Southeast Asian countries opting to receive treatment in private hospitals in Bangkok.

Thailand currently has no definition of a rare disease and no specific rare disease policies.

14.2 THAILAND HEALTH AUTHORITY

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.

14.3 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

14.4 ORPHAN DRUGS IN THAILAND

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 22 medical geneticists -- for a country of 68 million. Infant screening tests and orphan drugs are not widely accessible, and these treatments are usually not included on the country's National List of Essential Medicines (NLEM) or covered by the universal healthcare system. This makes the cost of treatment prohibitively expensive for most rare diseases. However, there have been some exceptions as imiglucerase, a drug with an FDA orphan designation for the treatment of Gaucher disease type I, is included on the NLEM for government reimbursement. Imiglucerase was included despite its exorbitant price as Thai authorities estimated that no more than 5 patients would require treatment per year. The addition of imiglucerase, an orphan drug, to the NLEM may be an indicator for more orphan drugs to be added to the NLEM in the future.

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.

14.5 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 which has come into effect on January 1, 2017. 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.

There is currently no specific orphan drug legislation in Vietnam, although rare disease management was made a priority in the new Pharmaceutical Law.

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
Phone: +84-4-3728-2496
Fax: +84-4-3754-3391
Email: cgat.dna@gmail.com
Website: http://cgat.vn/Sites/Web/en-US/Home

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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