ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

An Insight on Regulations Governing Orphan Diseases and Drugs

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ABSTRACT

The drugs or biological products for the diagnosis, treatment, or prevention of a rare disease or condition are orphan drugs. Even though the drugs intended to treat common disease where revenue is not expected by pharmaceutical manufacturer are as well categorized as orphan. United State of America (USA) was the first nation to propose a legal framework to encourage development and availability of orphan drugs. The Orphan Drug Act (ODA) was passed on January 28, 1983, which was an amendment of Federal Food, Drug and Cosmetic Act of 1938, to stimulate the research, development, and approval of products for orphan diseases. The regulation for orphan drugs varies in different countries. Several benefits are offered to the pharmaceutical manufacturer of orphan drug includes tax incentives for clinical research, exemption from application filing fees, grant for Phase I and II clinical trials and marketing exclusivity for a specific period of time. These benefits have motivated the pharmaceutical industries to discover new drug molecules offering a new hope to the patients with rare diseases. The current review talks about the various features of orphan drug regulations in USA, Australia, Japan and Europe.

Keywords: Orphan disease, orphan drug, regulation, rare disease, neglected disease, Orphan drug act

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ISSN: 0975-8585

INTRODUCTION

An orphan or rare disease may be defined, in United States of America (USA), one that affects less than 200,000 people in the US or one that affects greater than 200,000 people but for which there is no expectation that the cost of the development of the drug and making it available will be recovered from sales of that drug to poor affected population [1]. The orphan diseases, affect only a small numbers of people, are generally neglected by doctors viz Fabry's disease, alveolar echinococcosis, variant renal cancer, high myopia, endometrial cancer and tobacco addiction [2]. The designation of orphan disease varies in different countries depending upon the ratios viz. EU: 5 per 10,000 individuals, USA: 7.5 per 10,000 individuals, Japan: 4 per 10,000 individuals, Australia: 1 per 10,000 individuals [3]. Almost 5,000 to 8,000 distinct rare diseases (Table 1) exist today, affecting 6% to 8% of the population in the European Union. Symptoms of some rare diseases may appear at birth or in childhood, including infantile spinal muscular atrophy, lysosomal storage disorders, patent ductus arteriosus (PDA), familial adenomatous polyposis (FAP) and cystic fibrosis. A few rare diseases are the result of infections (bacterial or viral) and allergies, or are due to degenerative and proliferative causes. Medical and scientific knowledge about such is lacking. Every week approximately five new diseases are explained in the medical literature [4].

Table 1: List of some orphan diseases [5]

Acrocephalosyndactylia	Acrodermatitis
Addison Disease	Adie Syndrome
Alagille Syndrome	Amylose
Amyotrophic Lateral Sclerosis	Angelman Syndrome
Angiolymphoid Hyperplasia with Eosinophilia	Arnold-Chiari Malformation
Arthritis, Juvenile Rheumatoid	Asperger Syndrome
Bardet-Biedl Syndrome	Barrett Esophagus
Beckwith-Wiedemann Syndrome	Behcet Syndrome
Bloom Syndrome	Bowen's Disease
Brachial Plexus Neuropathies	Brown-Sequard Syndrome
Budd-Chiari Syndrome	Burkitt Lymphoma
Carcinoma 256, Walker	Caroli Disease
Charcot-Marie-Tooth Disease	Chediak-Higashi Syndrome
Chiari-Frommel Syndrome	Chondrodysplasia Punctata
Colonic Pseudo-Obstruction	Colorectal Neoplasms
Craniofacial Dysostosis	Creutzfeldt-Jakob Syndrome
Crohn Disease	Cushing Syndrome
Cystic Fibrosis	
Hirschsprung Disease	Histiocytic Necrotizing Lymphadenitis
Histiocytosis, Langerhans-Cell	Hodgkin Disease
Horner Syndrome	Huntington Disease
Hyperaldosteronism	Hyperostosis, Diffuse Idiopathic Skeletal
Inappropriate ADH Syndrome	Intestinal Polyps
Kartagener Syndrome	Kearns-Sayre Syndrome
Klippel-Feil Syndrome	Klippel-Trenaunay-Weber Syndrome
Kluver-Bucy Syndrome	Korsakoff Syndrome
Lafora Disease	Lambert-Eaton Myasthenic Syndrome

Landau-Kleffner Syndrome	Langer-Giedion Syndrome
Leigh Disease	Lesch-Nyhan Syndrome
Leukodystrophy, Globoid Cell	Li-Fraumeni Syndrome
Long QT Syndrome	
Machado-Joseph Disease	Mallory-Weiss Syndrome
Marek Disease	Marfan Syndrome
Meckel Diverticulum	Meige Syndrome
Melkersson-Rosenthal Syndrome	Meniere Disease
Mikulicz' Disease	Miller Fisher Syndrome
Mobius Syndrome	Moyamoya Disease
Mucocutaneous Lymph Node Syndrome	Mucopolysaccharidosis I
Mucopolysaccharidosis II	Mucopolysaccharidosis III
Mucopolysaccharidosis IV	Mucopolysaccharidosis VI
Multiple Endocrine Neoplasia Type 1	Munchausen Syndrome by Proxy
Neuroaxonal Dystrophies	Neuromyelitis Optica
Paralysis	Pelizaeus-Merzbacher Disease
Pemphigus, Benign Familial	Penile Induration
Pericarditis, Constrictive	Peroxisomal Disorders
Peutz-Jeghers Syndrome	Pick Disease of the Brain
Pierre Robin Syndrome	Pigmentation Disorders
Pityriasis Lichenoides	Polycystic Ovary Syndrome
Polyendocrinopathies, Autoimmune	Prader-Willi Syndrome
Rett Syndrome	Reye Syndrome
Sandhoff Disease	Sarcoma, Ewing's

ORPHAN DRUGS

Table 2: Classification of orphan drugs

Type	Detail	Expected profits	Available medication
I	Little / no commercial benefit	Poor	Inadequate
II	Commercial benefit	Good to excellent	Inadequate
III	For rare disease that can currently be treated	Variable	Adequate
IV	Unprofitable for a common disease	Poor	Inadequate
V	Orphan for both rare and common disease	Variable	Variable

European regulation defines orphan medicinal products as those for which it can be established that either intended for the diagnosis, prevention or treatment of a life-threatening or chronically unbearable condition affecting not more than five out of ten thousand people; or intended for the diagnosis, prevention or treatment of a life-threatening, seriously unbearable or serious and chronic condition and that, without incentives, they are unlikely to generate sufficient revenues to justify the necessary investments[6]. Orphan drugs are defined as drugs intended to treat either a rare disease or a widespread disease where manufacturer cannot expect to make profits. Drugs and vaccine for tropical diseases are orphan drugs because patient sufferings from these diseases, although numbering tens of millions, are too poor to pay

the price of medications. Vaccines are virtual orphans and also called economic orphans. The number of vaccines introduced in the market has decreased drastically in the recent years. The growth hormone (GH), earlier obtained from corpses, manufactured by recombinant technology is still classified as orphan drug in USA. The Orphan Drug Act USA defines an orphan drug as a drug or biological product for the diagnosis, treatment, or prevention of a rare disease or condition. Orphan drugs available to treat rare diseases are a heterogenous group. Table 2 represents a classification of five categories of orphan drugs based on their commercial potential and the availability of adequate treatment [7,8].

Numbers of drugs have crossed from the type1 to type III categories over the period. These include Wilson's disease, which can be treated now a days with penicillamine, zinc & triethylenetetramine and rare bacterial diseases that can be treated with antimicrobials. Type I and III orphan drugs are usually the most difficult ones to find sponsors for if the drugs are known to have activity but are yet not marketed. These drugs can become profitable type V drugs if found to be effective in treating a common disease[9].

ORPHAN DRUG REGULATIONS

Inaccessibility of specific treatment for orphan disease leads the patient and their family into mental stress & depression. Many diseases lacking specific therapy are important targets for unreliable therapy. Thus the unproven therapies and wrong beliefs prevail in seek out of some relief. Orphan drugs generally follow the same regulatory development path as any other pharmaceutical product, in which testing focuses on pharmacokinetics and pharmacodynamics, dosing, stability, safety and efficacy. However, some statistical burdens are lessened in an effort to maintain development momentum. For example, orphan drug regulations generally acknowledge the fact that it may not be possible to test 1,000 patients in a phase III clinical trial, as fewer than that number may be afflicted with the disease in question. Since the market for any drug with such a limited application scope would be small and thus largely unprofitable, government intervention is often required to motivate a manufacturer to address the need for an orphan drug.

USA was the first nation to propose a legal framework to encourage development and availability of orphan drugs. The Orphan Drug Act (ODA) was passed on January 28, 1983, which was an amendment of Federal Food, Drug and Cosmetic Act of 1938, to stimulate the research, development, and approval of products that treat orphan diseases. ODA exists in various countries like USA, Japan, Singapore, Australia, Canada, France, Sweden, and United Kingdom. The basis of the initiative of other countries being the US ODA, with variations like marketing exclusivity rights to the marketing company for 7 years in USA, 10 years in Japan, and 5 years in Australia [10].

ISSN: 0975-8585

THE USA ORPHAN DRUG ACT

The U.S. Orphan Drug Act was signed in 1983 and provided incentives for the pharmaceutical industry to develop drugs that otherwise had minimal commercial return on investment, but which are necessary, and often life-saving, for patients with rare diseases [11]. The Orphan Drug Act is codified in 21 CFR Part 316. Since 1983, Congress has amended the Orphan Drug Act several times. Amendments to the Orphan Drug Act were passed in 1984, 1985, 1988, 1990 and 1992 [12].

The distinctive purpose of the 1983 Orphan Drug Act was to provide incentives in the development of drugs for the treatment of rare diseases that would normally be unprofitable or unpatentable. The manufacturers had to demonstrate, to qualify for orphan drug status, that the development of a particular orphan drug would be unprofitable. As per the amendment to the Act in 1984, to qualify for orphan drug status, a rare disease or condition was defined as any disease or condition either affecting less than 200,000 persons in the United States, or affecting more than 200,000 persons in the United States, but for which there is no reasonable expectation that the sales of the drug will recover the costs. Prior to this amendment, a drug sponsor was required to provide financial information regardless of the size of the proposed target patient population [13].

In 1985, the act was amended again, to extend marketing exclusivity for both patentable and unpatentable products. The purpose was to protect those products that were patentable, but whose patents would expire before or shortly after marketing approval. Many of these drugs were biotech drugs that had difficulties in obtaining patents. The earlier assumption about most orphan drugs being unpatentable was found to not always be true. Patents had been issued for many potential orphan products, but because of prolonged research, the patent protection had sometimes expired before marketing approval was obtained.

In 1988, an amendment to the Act changed the requirement for submitting applications for orphan drug status. The application for orphan drug designation now has to be made prior to the submission of an application for marketing approval, New Drug Application (NDA) or Product License Application (PLA). Prior to the1988 amendment, the designation request could be filed at any time before the U.S. Food and Drug Administration's (FDA) approval to market the product.

The Orphan Drug Act provides a number of specific incentives for sponsors of orphan designated drugs. These include:

- The FDA modernization act of 1997 exempted designated orphan drug products from paying new drug application fee. It also included a provision for orphan product sponsors to seek waivers for post approval annual establishment and product fees.
- Seven years of exclusive marketing rights to the sponsor of a designated orphan drug product for the designated indication once it receives approval to market from the FDA.

- A credit against tax owed for up to 50% of qualified clinical research expenses incurred in developing a designated orphan product. This tax credit has a carry-back/carry-forward provision, which allows the sponsor to carry the excess credit back one tax year if they are unable to use part or all of the credit because of tax liability limits, and to then carry any additional unused credit forward for up to 20 tax years after the year of the credit. This later provision is important to start-up companies that may not make any profits until the drug in question is on the market [14].

Orphan drug designation:

The OOPD evaluate requests for orphan drug designation, and once a drug is designated, acts as an internal FDA advocate interfacing with the FDA review division to help facilitate progress. The OOPD is separate from the FDA therapeutic review divisions. The review divisions are still responsible for evaluating data in terms of risk-versus-benefit considerations and approving drugs for marketing. Second, the OOPD is responsible for evaluating, awarding, and monitoring the progress of orphan drug grants. A sponsor may request orphan drug designation for a previously unapproved drug or a new indication for an already marketed drug. The drug product may be a new formulation and the requisite information for a new drug product required by International Conference on Harmonisation (ICH)/FDA would need to be provided in a marketing application. If the sponsor is able to provide valid evidence that their drug may be clinically superior to the drug already has orphan drug status, the new drug can be designated as orphan drug. In either of the above scenarios, the sponsor would need to include patent certification in the marketing application that demonstrates that there are no patent infringement issues. If a valid request for orphan designation is made, the OOPD can award an orphan drug designation for the same drug for the same rare or condition to more than one sponsor [15].

More than 350 products including the biological for the treatment of rare diseases have been designated orphan status since 1983 in USA [16]. FDA has given orphan drug status for Rivax™, a vaccine for prevention of a life threatening rare disease ricin toxication, to the Soligenix Inc., NZ in January 2011 [17].

JAPAN ORPHAN DRUG REGULATION

After the first national orphan drug policy in United States, It took ten years for the second country, Japan, to follow with a similar, although less generous amendment to its drug regulatory and taxation laws. On 1 October 1993, the Japanese government revised the pharmaceutical law by introducing special provisions relative to research and development of orphan drugs. According to provisions, orphan drug status can be granted to a drug, provided it fulfills the two criteria. The disease for which use of the drug is claimed must be incurable. There must be no possible alternative treatment; or the efficacy and expected safety of the drug must be excellent in comparison with other available drugs. The number of patients affected by this disease in Japan must be less than 50000 on the Japanese territory, which

corresponds to a maximal incidence of four per ten thousand. Japanese orphan drugs system offered new opportunities both for multinational and small-size and medium-size companies. Public institutes and universities, and biotechnology companies are less active than in the USA.

Orphan drugs labeling:

The orphan drug status is granted by the Ministry of Health, Labour and Welfare (MHLW). Scientific examination by a subcommittee of the Medicinal Products Committee is followed by special committee. The orphan drug designation may be granted to the sponsors by authorities on submission of the estimated size of patient population, non-clinical and early phase clinical study, and Development protocol. The orphan drug status that has been granted may be withdrawn if the conditions of the license are no longer fulfilled. The Japanese government support for research and development of orphan drugs by benefiting from a fast-track marketing authorization procedure. The law requires priority of evaluation of applications made for indications concerning rare diseases. The Organization for Pharmaceutical Safety and Research provides pharmaceutical companies launching orphan drugs with a consultation on development protocols and some advice concerning the preparation of approval applications. The registration validity period, which varies from four to six years for traditional drugs, is extended to 10 years for orphan products.

Some government funds, such as the Drug Fund for Side-Effects Relief and Research Promotion, guarantee financial assistance to cover a proportion of the expenditure devoted to research and development of orphan drugs. The Japanese authorities reimburse up to 50% of the development costs. A 6% tax reduction for Research and Development expenses is granted, other than those coming from funding grants and within the limit of 10% of company tax. Companies making profits on sales of orphan drugs must return a proportion of the subsidy granted as a contribution to these funds [18].

AUSTRALIAN ORPHAN DRUGS ACT

The Australian orphan drugs policy was set up in 1997. This orphan drugs program aims to ensure the availability of a greater range of treatments for rare diseases and allows the Australian Therapeutic Goods Administration (TGA) to use information from the US Food and Drug Administration (FDA) Orphan Drugs Program as part of the Australian evaluation process. To be eligible for designation as an orphan drug the product must not have been rejected on safety grounds by the TGA, the Food and Drug Administration of the United States of America (FDA), the Medicines and Healthcare Products Regulatory Agency of the United Kingdom (MHRA), the Therapeutic Products Directorate of Canada (TPD), the Medical Products Agency of Sweden (MPA), the Medicines Evaluation Board of the Netherlands (MEB) or the European Medicines Agency (EMEA) for use for the disease in question. Orphan designation is intended for drugs which aim to treat diseases with a prevalence of 2000 patients or less in the Australian population (18 million)/ a maximal of twelve to per ten thousand. Another

alternative criterion which leads to orphan designation consists in combining the fact that the drug is not commercially available, when used in the patient population it is indicated for.

Once orphan designation is granted, the TGA waives the evaluation fees, thus removing a major obstacle to making these crucial drugs available. A distinct evaluation pathway for processing orphan drugs is also set up. One of the programme's important purposes is the possibility of making drugs available to treat leprosy and trachoma which affect the aboriginal population. The main characteristic of the Australian Orphan Drugs Program is that it is based upon a close collaboration of the TGA with the US FDA. The Australian programme takes into account the FDA's orphan drugs evaluations. Additional criteria are also established for identifying and evaluating orphan drugs in Australia which have not been evaluated in the USA or do not meet the US criteria [19].

The main characteristics of the orphan drug policy in Australia are:

- A legal framework for orphan drug designation ;
- Waiver of application and evaluation and no annual registration fees ;
- Five-year exclusivity.

Table 3: Some orphan designated drugs across Australia in year 2010

Afamelanotide	*Ex vivo* cultured adult human mesenchymal stem cells	Romidepsin
Bosentan	Human hepatitis b immunoglobulin	Sunitinib malate
C 1 esterase inhibitor	Immunoglobulin - antithymocyte (rabbit)	Tadalafil
Catumaxomab	Mycophenolic acid	Terlipressin acetate
Duodopa (levodopa / carbidopa)	Octreotide	Tobramycin
Everolimus	Peginterferon alfa-2b and ribavirin	Vandetanib

Regarding the funding of orphan drugs, the TGA covers all the costs of the orphan drug designation process, and then balances its expenditures with other components of the health care system overall budget. The health-care financing system may be an issue in the delivery of orphan drugs to patients. The country has a pharmaceutical benefits scheme, which provides subsidies to make some drugs affordable. In Australia, R&D is not supported by grants or tax incentives. There is no specific law concerning intellectual property for orphan drugs. The legal status is applied to orphan drugs as for any other drug registered for supply in Australia. On the other hand, registration fees are covered by the Therapeutic Goods Administration [20]. Table 3 shows a few among the several drugs designated orphan status in Australia [21].

EUROPEAN ORPHAN DRUG ACT

Efforts have been jointly made at national and European levels by industry and health authority, European Medicines Evaluation Agency (EMEA), in order to offer the incentives required to stimulate the development of orphan drugs. The goal was to rapidly make available,

for rare diseases, drugs with a level of quality equivalent to that required for any other drug. A policy was implemented much later in Europe than in the USA. The reason lies mainly in the fact that its territory is split-up and its competencies as regard to health are scattered. Since 1 January 1995, with the new system of EU marketing authorisation that is valid for the whole territory and the free circulation that goes with it, Europe can be considered now as a territory with a population of about 377 million inhabitants that is a population greater than that of the United States where a common regulation is enforced. On 16 December 1999, the European Parliament and the Council adopted regulation (CE) No. 141/2000 on orphan drugs [22]. The goals were to encourage the pharmaceutical and biotechnological industry to develop and market orphan drugs, create a Committee of Orphan Medicinal Products (COMP) within the European Medicines Evaluation Agency (EMEA). This committee is responsible for studying the applications for orphan designation and to advise and assist the Commission in discussions on orphan drugs [23].

The COMP consists of persons appointed by the European Member States, and 3 are appointed by the European Commission to liaise with the Committee of Propriety Medicinal Products (CPMP) responsible for scientific evaluation of medicinal products within EMEA as well as three representatives of patient associations. The participation of patient representatives in the COMP has been very positive for the process of developing therapies for rare diseases in Europe [24].

Companies with an orphan designation for a medicinal product benefit from incentives such as:

- Protocol assistance (scientific advice for orphan medicines during the product development phase);
- Direct access to centralised marketing authorisation
- 10-year marketing exclusivity;
- Financial incentives (fee reductions or exemptions);
- National incentives detailed in an inventory made available by the European Commission.

Since 1 February 2009, orphan medicinal products are eligible for the following level of fee reductions:

- Full reduction for protocol assistance and follow-up
- Full reduction for pre-authorisation inspections, 50% reduction for new applications for marketing authorisation to applicants other than small and medium-sized enterprises;
- Full reduction for new applications for marketing authorisation only to small and medium-sized enterprises;
- Full reduction for post authorisation activities including annual fees only to small and medium sized enterprises in the first year after granting a marketing authorization.

According to European regulation No. 141/2000, only drugs for human use can be designated as orphan drugs. Therefore it does not concern veterinary medicines, medical devices,

nutritional supplements and dietary products. Drugs designated as orphan are entered in the Community register for Orphan Medicinal Products [25].

Availability of orphan drugs in Europe:

The granting of marketing approval does not mean the drug is available throughout all the European countries. The marketing approval holder must decide in advance on its commercial status within every country and the drug will then go through numerous steps in each country in order to condition its management. Drugs which are exclusively used in hospitals are, following positive mention by the Commission, registered on the list of admitted products for the community. They price nothing. Despite joint efforts, the heterogeneous approaches among countries make patients access to orphan drugs more complex. Several orphan drug designation have been given for rare diseases (Table 4 shows a few among that) since the regulations framed in Europe and entered in Community register for Orphan Medicinal Products.

Table 4: Few Orphan diseases for which the orphan products designated in europe during 2010

Hepatocellular Carcinoma	Primary Myelofibrosis	Cystic Fibrosis
Acute Myeloid Leukaemia	Post-Essential Thrombocythaemia Myelofibrosis	Primary Biliary Cirrhosis
Ovarian Cancer	Medulloblastoma	Glioma
Mantle Cell Lymphoma	Idiopathic Pulmonary Fibrosis	Low-Flow Priapism
Acute Myeloid Leukaemia	Perinatal Asphyxia	Rhodopsin-Linked Retinitis Pigmentosa
Post-Polycythaemia Vera Myelofibrosis	Acute Myeloid Leukaemia	Mucopolysaccharidosis, Type IIIA (Sanfilippo A Syndrome)

The overall scenario of the orphan drug policies across the globe differ in several aspects. Table 5 narrates a comparison of the policies for orphan drug in some countries [27, 28].

ORPHAN DRUG ACT IN INDIAN PERSPECTIVE

The established and developed countries have captures the importance of orphan drug regulation offering several incentives along with fast approval process for the pharmaceutical manufacturers. The developing countries like India would be affected a lot during third world war with rare disease. Need for such an act is evident, initiative from the Indian Pharmacists and the Government to implement such Laws would strengthen the health infrastructure, manufacturers and provide relief to the numerous rare disease sufferers across the country. A group of pharmacologists at a conference held by the Indian Drugs Manufactures Association (IDMA) in 2001, requested the Indian Government to establish the Orphan Drug Act in India [29]. If such legislation could be implemented, it will be a benefit not only to pharmaceutical and biotechnological Industry but will also bring relief to the unlisted very possibly large groups of rare disease sufferers, in the country. The national orphan drug regulation should offer

lucrative incentive, economic outcome and market exclusivity rights to the rare drug manufacturer to enjoy the reasonable profit and interest for investment in the R&D of rare drugs [30].

CONCLUSIONS

The success of orphan drug designation for neglected rare diseases shows that companies using orphan drug programs can generate profits and recoup their R&D investments even with relatively small markets in the developed world. The orphan drug designation mainly encourages investments and initiatives by small science-oriented companies. In general, orphan drugs have been developed by small biotech firms focused on niche markets or by academic investigators combining solid scientific expertise in a specific medical area with good entrepreneurial skills. The orphan drug designation should be promoted in various countries, not having their regulations for such categories of diseases, to promote the treatment for sufferers with rare diseases.

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