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Orphan Drug Act: History, Perspective and Challenges for Future

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ABSTRACT

An orphan drug is a pharmaceutical agent that is used to treat a rare medical condition (viz., Huntington's disease, myoclonus disease, Tourette syndrome etc.). They receive little attention from pharmaceutical companies as the small patient population could not justify the huge investment required for drug development. In the last 20 years, orphan drug act has been adopted in several countries around the world (USA, Japan, Australia, and the EU) and has successfully promoted R&D investments to develop new pharmaceutical products for the treatment of rare diseases, but it faces future challenges like returns on the huge R & D costs, funding sources and initiatives for development of orphan drugs.

Keywords: Rare Diseases, Incentives, Marketing Exclusivity, Challenges.

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INTRODUCTION

Diseases that manifest in patient populations representing at the maximum 6–8% of the world population are defined as “rare diseases” or “orphan diseases”. An orphan drug is a pharmaceutical agent that is used to treat a rare medical condition (viz., Huntington’s disease, myoclonus disease, Tourette syndrome etc.), the condition itself being referred to as an orphan disease. The spiraling cost of drug development in tune with stringent regulations, coupled with the low return on investment, often tends to discourage pharmaceutical innovators from developing products for extremely small patient populations. 80% of rare diseases have been identified to genetic origins. Other rare diseases are the result of infections (bacterial or viral) and allergies, or are due to degenerative and proliferative causes[3].

Some of the disincentives involved are lack of funding, and the multiple areas of expertise are required. A lot of initiatives are taken up by various countries via, formation of the National Organization for Rare Diseases, enactment of the Orphan Drug Act, development of a grant program to fund orphan drug development, the formation of the National Institutes of Health Office of Rare Diseases, and the passage of orphan drug legislation. Although Progress is made, 300 orphan drugs and devices approved in the last 25 years are still only a drop in the bucket compared with the many thousands of orphan diseases. Before orphan drug act, till 1966, industries had sponsored 34 marketed and 24 experimental orphan drugs. It has sponsored 39 of 42 marketed orphan products in the 7 years since the Act. The number of rare diseases for which no treatment is currently available is estimated to be between 4,000 and 5,000 worldwide[3].

Revenues:

The global orphan drugs market reached $85 billion in 2009 growing from $59 billion in 2006 from $55 billion in 2005. The market is expected to grow at a compound annual growth rate (CAGR) of nearly 6% to reach $112 billion by 2014.

Biological drugs account for a major share (64.3%) of the orphan drug market with sales of $55 billion in 2009 as compared to $35 billion in 2006 and $30.2 billion in 2005. The size of the biological orphan drug market is projected to grow at a 7% CAGR to reach $76 billion by 2014.

Orphan drugs for the cancer sector generated the largest amount of revenues, $30.6 billion in 2009, and accounting for 36% of the market. Revenues for cancer-related orphan drugs are expected to grow at a CAGR of 10% to reach $50 billion in 2014[1]. A survey was conducted describing increase demand for the orphan drugs from year 2008-2011, shown in figure 1 and table 1.

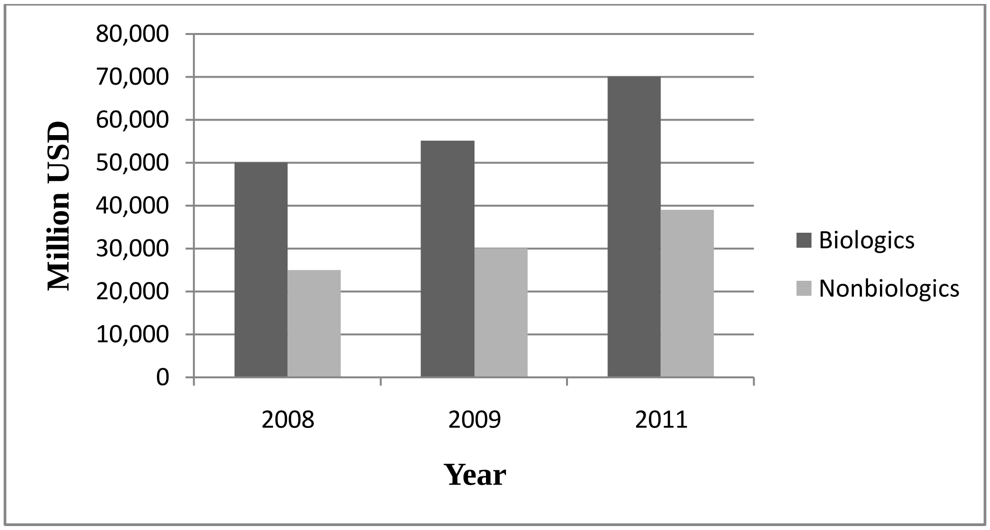


Figure-1: global orphan drugs demand

The above figure 1 describes the increasing demand for the orphan drugs from year 2008-2011[9].

Table -1: Global orphan drugs demand by value (in million USD).

	2005	2006	2011	CAGR%
Biologics	30,200	35,300	53,400	9
Non Biologics	24,300	23,400	28,400	4
Total	54,500	58,700	81,800	7

UNITED STATES

Any drug developed under the Orphan Drug Act of 4th January 1983 (ODA) is an orphan drug. The ODA is a federal law concerning rare diseases (orphan diseases) that affect fewer than 200,000 people in the United States or are of low prevalence (less than 5 per 10,000 in the community)[3].

Congress amended the Act in 1984, 1985, and 1988. In 1992 FDA issued its final regulations establishing standards and procedures for granting orphan status. The final rule recognizes exclusive marketing rights as the major incentive in the Orphan Drug Act and explains the criteria a sponsor must meet to prove clinical superiority and enter the market when another product if the same category already has marketing exclusivity[6].

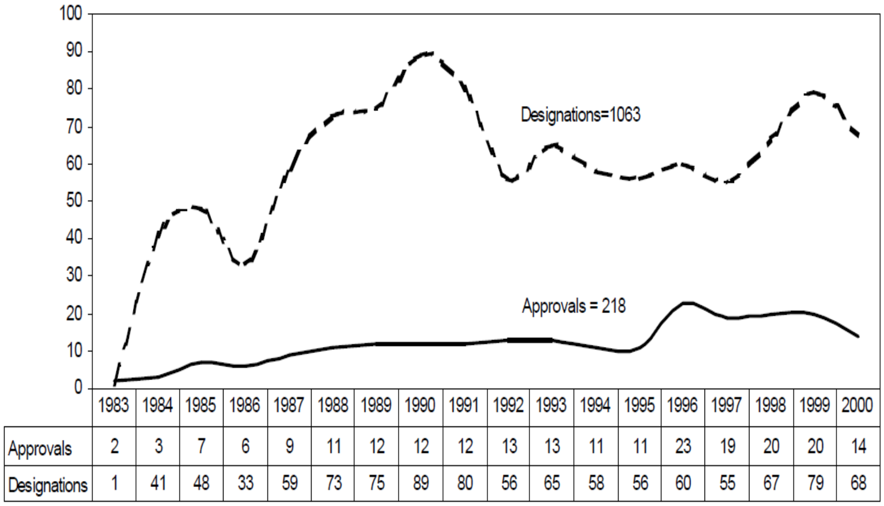
Incentives that were provided by the Orphan Drug Act are:

1. 7-year market exclusivity for the drug for the indication.
2. Availability of orphan product development grants.
3. Tax credits equal to 50% of the expenses for clinical (not preclinical) development costs.
4. Protocol assistance[6].

The Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) review applications for marketing approval. To obtain an orphan status, sponsors must submit an application to the Office of Orphan Products Development with the following important information.

- Description of the disease for which use of the drug is claimed and the intended conditions of use.
- The sponsor should provide the size and other chief characteristics of the population likely to be treated in the USA.
- Description of the drug and its known risk: benefit ratio.
- A summary of the principal preclinical and clinical data concerning use of the product in the claimed indication, as well as basic documentation, should be provided, and all available information, published or otherwise, must be supplied.
- Finally, if the product is claimed not to be profitable for 7 years following its approval for marketing, an estimate must be given of the cost of development and distribution of the drug, as well as an assessment of potential sales in the USA, confirming the absence of commercial viability of marketing the drug in specific cases.

The Office of orphan drug will try to respond within 60 working days of receiving an application for orphan status, the process may take longer if the office needs more information from the sponsor. After receiving the orphan designation and conducting more research, a sponsor may seek marketing approval if the drug proves safe and effective in clinical trials[6]. There was an increased scenario of designations and approvals of orphan drugs in US after the implementation of the orphan drug act 1983, depicted graphically in figure 2.



	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
Approvals	2	3	7	6	9	11	12	12	12	13	13	11	11	23	19	20	20	14
Designations	1	41	48	33	59	73	75	89	80	56	65	58	56	60	55	67	79	68

Figure-2: Total orphan designations and approvals

This figure depicts the increased scenario of designations and approvals of orphan drugs in US after the implementation of the orphan drug act 1983.

EUROPE

In 2000, the European Union (EU) also adopted regulations relating to this important area of drug development and public health. Efforts have been jointly made at national and European levels by industry and health authorities (EMEA - European Medicines Evaluation Agency), 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. Since then, more than 850 orphan drug designations have been granted by the European Commission based on a positive opinion from the Committee for Orphan Medicinal Products (COMP) and more than 60 orphan drugs have received marketing authorization in Europe[7].

Table-2: Access of orphan drugs in some European countries.

Country	Early access	Access	Comments
Germany	No	Easy	Nothing particular
Austria	UC/NP	Slow	Nothing particular
Belgium	UC/NP	Slow	Nothing particular
Denmark	UC/NP	Complex	Nothing particular
Finland	UC/NP	Complex	Nothing particular
France	TUA	Rapid	Coordination level at OMS level
Spain	UC/NP	Classic	Nothing particular
Greece	UC/NP	Classic	Nothing particular
Ireland	UC/NP	Classic	Nothing particular
Italy	TUA	Classic	Nothing particular
Luxembourg	UC/NP	Classic	Nothing particular
Netherlands	UC/NP	Classic	Improvement to be discussed
Portugal	Depends on the case	Depends on the case	Special funds awarded
UK	UC/NP	Slow	Considered as expensive
Sweden	UC/NP	Easy	Nothing particular

UC: Use Compassionate, NP: Nominative Base of Patients, TUA: Temporary Use Authorization[4].

The applicants are generally advised to have a pre-submission meeting with the EMEA Secretariat. On receipt of a valid application, the COMP appoints one of its members and a professional staff member of the EMEA Secretariat to act as coordinators (day 0). The two coordinators prepare a joint assessment report for discussion at the following COMP meeting (day 30). If the COMP is satisfied that the criteria are met, a positive opinion is issued. More often, there are issues that require clarification and a list of questions or issues to be addressed is sent to the applicant. The responses are assessed by the coordinators and discussed at the next meeting (day 60). If there are still any outstanding issues, these can be dealt with during an oral hearing on day 90, when an opinion is issued. In case of a negative opinion, the applicant has full appeal rights[5]. Because of differences in legislation, facility and rapidity to access orphan drugs is not the same in all the European countries, for example access to few of the countries is indicated in table 2[4].

JAPAN

On 1st October 1993, the Japanese government, Ministry of Health, Labor and Welfare (MHLW) revised the pharmaceutical law by introducing special provisions related to research and development of orphan drugs. In April 2004, the new Pharmaceutical and Medical Devices Agency (PMDA), under the supervision of MHLW, took over the operation of orphan product promotion from the Ministry's Organization for Pharmaceutical Safety and Research, also known as 'KIKO'. According to these new provisions, orphan drug status can be granted to a drug, provided it fulfills the following two criteria.

- There must be no possible alternative treatment for the disease for which use of the drug is claimed 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 50,000 on the Japanese territory, which corresponds to a maximal incidence of four per ten thousand[4].

Incentives

Apart from a reduced fee for Japanese marketing authorization application, other incentives offered include

(i) Consultation and advice for development,

(ii) An orphan products development grant (up to 50% of the R & D cost per year for a maximum of 3 years after designation)

(iii) Authorization for tax deduction

(iv) Fast-track review for approval and

(v) Extension of the reexamination period from a normal 5-year period to a 10-year period for orphan drugs and a 7-year period for orphan devices[4].

The MHLW receives and determines an application for designation of a drug as orphan and the Centre for Product Evaluation of the PMDA is responsible for specialist consultation and advice (fees are chargeable). The procedure for designation involves an application (may be made by telephone or facsimile) for a pre-designation hearing. The Evaluation and Licensing Division of the MHLW accepts the application and a contact person is appointed who arranges a date for the pre-designation consultation. The pre-designation hearing usually lasts for 30 minutes. Following this, if there are no particular problems, the applicant submits a formal application for designation to the Evaluation and Licensing Division. The PMDA evaluates the application and, if the product is determined appropriate for designation, the MHLW asks the opinion of the Pharmaceutical Affairs and Food Sanitation Council. When the Council determines that the criteria for designation are met, the MHLW designates the product as an orphan product and the applicant is notified accordingly. The public is informed of the newly designated orphan product by notification from the Director of Evaluation and Licensing Division in the government gazette[5].

As of April 2004, 168 orphan products were designated and, of these, 96 have been approved for marketing. The corresponding figures for orphan devices were ten and four, respectively[5].

AUSTRALIA

The Australian orphan drugs policy was set up in 1998. In Australia, orphan drugs are drugs used to treat diseases or conditions affecting fewer than 2,000 individuals at any one time (0.2%). The Australian Orphan Drugs Program helps manufacturers to overcome the high cost of marketing drugs which have proved to be commercially not viable because of small patient population[3].

The main characteristic of the Australian Orphan Drugs Program is that it is based upon a close collaboration of the Therapeutic Goods Administration (TGA) with the US-FDA. The main incentives of the orphan drug policy in Australia are

1. A legal framework for orphan drug designation
2. Waiver of application and evaluation and no annual registration fees
3. Five-year exclusivity (under consideration by the Australian jurisdiction)[4].

Once orphan designation is granted, the TGA waives the evaluation fees, thus removing a major impediment to making these crucial drugs available and then balances its expenditures with other components of the health care system overall budget[4].

DEVELOPING COUNTRIES

The need for orphan drugs has been on the rise in recent years, and is especially so in developing countries. In many cases, nobody is investing in developing better drugs for diseases that affect these countries. With giant pharmaceutical companies such as Pfizer, laying off workers as part of cost-cutting, they are also trimming research costs focused on revenue and barely breaking even. Resultantly, research and development in the smaller markets tend to get overlooked[8].

Within the framework of world health organization (WHO), the Children's Vaccine Initiative (CVI), set the development of vaccines with commercial prospects as a priority. This cost-oriented definition reflects the difficulty of developing drugs for tropical diseases, even the most prevalent ones such as malaria[4].

Other non-economic factors could justify an industry's decision to develop and market an orphan vaccine:

1. The desire to enhance the company's ethical profile, by fulfilling a medical or social need
2. The capacity to develop, product and market a drug ;
3. A larger company strategy (e.g. extension of a product range)[4].

For example in India, the need for such an act is thus evident from the initiative by the Indian Pharmacists and the Government to implement Laws, which would strengthen the health infrastructure and provide relief to the numerous rare disease sufferers throughout the country. A group of pharmacologists at a conference held by the Indian Drugs Manufactures Association in 2001 requested the Indian Government to institute the Orphan Drug Act in India[3].

Challenges in Access to and Affordability of Medicines for Rare Diseases

Despite the progress, no effective and safe treatment is available for many rare diseases. Furthermore, when treatments are available, obstacles are encountered that hinder access and use of these drugs.

- **Challenges in assessing clinical relevance and cost effectiveness:** The methodology for evaluating orphan drug treatments is often still in an experimental phase, hampering positioning in clinical practice[3].
- **Lack of knowledge and training**: For many rare diseases, available information is inadequate. Health professionals often lack appropriate training and awareness to be able to diagnose and adequately treat these diseases[3].
- **Deficient diagnostic systems**: For many diseases, no diagnostic methods exist, or diagnostic facilities are unavailable. In these cases, diagnosis may be problematic. Consequently, validity, coding, and reproducibility are problematic. Although the pace of gene discovery for rare genetic diseases has accelerated during the past decade, in part, due to the success of the Human Genome Project, translation of these discoveries to clinical utility still lags behind[3].
- **High prices**: Prices of orphan drugs per treatment episode can be very high. For example, the cost of treatment with enzyme replacement therapies may reach more than

US$150,000 per treatment year. The affordability of orphan drugs has become a major issue for payers and is thus a strong driver of tensions between the different stakeholders. Some companies have responded to this by developing programs to facilitate access to orphan drugs. These obstacles to treating rare diseases with orphan drugs exemplify and mirror the global debate of deficiencies in bringing new drugs to patients who need them[3].

- **Patent Protection and Product Liability**: Introduction of new vaccines relies heavily on the strategic use of intellectual property rights to reassure investors that a candidate vaccine will provide a fair return on invested funds. The lack of patent protection or legal framework for intellectual property rights in some developing countries interferes with the long-term viability of a vaccine. In Western countries, liability issues associated with a candidate vaccine and its intended population also affects development costs[2].

Various strategies, proposals, and recommendations for overcoming limitations inherent in orphan vaccine development and availability are[2.]

1. Provide information, prioritize, and secure demand

- ➢ Increase awareness of disease: set-up special interest groups (patients, parents, professionals), expert groups, and national forums
- ➢ Establish the suitability of vaccine prevention vs. other options: realistic comparisons of vaccination with patterns and costs of other alternatives
- ➢ Ensure political support for orphan vaccine initiatives and organize tripartite partnerships between public, private, and nongovernmental sectors.

2. Facilitate vaccine research and development and national/regional approvals

- ➢ Promote innovative research and development technologies that could be applied to blockbuster vaccines or, alternatively, promote low-cost traditional vaccine technologies.
- ➢ Encourage public/private sector links: academic/industrial research groups.
- ➢ Set international standards of quality, safety, and efficacy and define minimum amount of data required for licensure.
- ➢ Make recommendations on appropriate schedules, target ages.
- ➢ Promote national and regional ex-U.S. and European Community incentives on Orphan Drug Policies.
- ➢ Expand and harmonize orphan drug policies as part of the ICH process.

3. Ensure market/funding visibility, production and distribution

- ➢ Reduce investment risks for manufacturers by providing realistic demand estimates.

- Fund development of orphan vaccines for developing countries through various institutional bodies, nongovernmental organizations and foundations on the basis of target assistance for the neediest countries based on total gross national product
- Promote and support protection of intellectual property.
- Clarify compensation programs that may assume responsibility for liability.
- Establish manufacturing strategies, such as campaigning to subsidize orphan vaccine cost investments by large volume sales of EPI vaccines.
- Strengthen the vaccine distribution network for the targeted population[2].

Future of 'Orphan Drugs'

The future of the orphan drug industry will depend heavily upon the entry of biogenerics, since biologics account for over 50% of the orphan drug market. It can be expected that the orphan drug market growth will remain positive as more and more governments are taking action to promote this sector, especially in Asia[1].

Australia, Japan, Singapore, Taiwan, and Korea have already implemented legislation for promoting research on orphan drugs, India and New Zealand are in the process of establishing similar regulatory processes. With more countries adopting similar legislation, it can be expected that market potential will increase[1].

CONCLUSION

The orphan drug programs relating to rare diseases have met success only in some countries. In developing countries, condition is pathetic where the per capita income is less than $ 2-3, inadequate to boost pharmaceutical R & D. However, some provisions of the US and EU text may be admitting the need for more specific rule for evaluation of orphan drug and recognizing the existence of 'diseases of exception'.

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