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ORPHAN DRUGS: AN OVERVIEW AND REGULATORY REVIEW PROCESS

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ABSTRACT:

Orphan drugs are drugs or vaccines intended to treat, prevent or diagnose a rare diseases like Huntington's disease, myoclonus syndrome disease, Tourette syndrome, etc. definition of these are rare diseases varies widely but generally takes into account the occurrence of the disease, its severity, and the availability of alternate therapies. A rare disease is not found worldwide and depends on the laws and policies adopted by each state or country. A rare disease is not universal and depends on the legislation and policies adopted by each region or country. A rare disease is not universal and depends on the legislation and policies adopted by each region or country. In the last 35 years, ODA (Orphan Drug Act, 1983) has been adopted in several countries worldwide (USA, Australia, European Union, Japan, etc.) and has successfully promoted R and D investments to develop new pharmaceutical products for the treatment of rare diseases. The incidences of such diseases have been increasing at a greater pace than the speed with which drugs are researched and developed to treat such diseases. One of the major reasons is that the pharmaceutical industry is not very keen to research the development of orphan drugs as these drugs do not capture a bigger market. This is the current scenario in-spite of the various incentives provided in the orphan drug act. However, in this article, we have tried to focus on existing regulations and policies utilized by various countries namely USA, EU, Japan, and Australia. It has been noted, most importantly that the two largest populated countries- China and India, both lack national legislation for orphan medicines and rare diseases, which could have substantial negative impacts on their patient populations with rare diseases. One of the major reasons is that the pharmaceutical industry is not very keen to research the development of orphan drugs as these drugs do not capture a bigger market. This is the current scenario in-spite of the various incentives provided in the orphan drug act. However, in this article, we have tried to focus on existing regulations and policies utilized by various countries namely USA, EU, Japan, and Australia. It has been noted, most importantly that the two largest populated countries- China and India, both lack national legislation for orphan medicines and rare diseases, which could have substantial negative impacts on their patient populations with rare diseases.[1]

KEYWORDS: Orphan drugs, rare diseases, Huntington's disease, Treatment, Clinical.

INTRODUCTION:

Orphan drugs are medicines or vaccines intended to treat, prevent or diagnose a rare disease (viz., Huntington's disease, myoclonus disease, Tourette syndrome, etc.). The definition of rare diseases varies across jurisdictions but typically considers disease prevalence, severity, and existence of alternative therapeutic options. A rare disease is not universal and depends on the legislation and policies adopted by each region or country. A rare disease is not universal and depends on the legislation and policies adopted by each region or country. In the last 35 years, ODA (Orphan Drug Act, 1983) has been adopted in several countries worldwide (USA, Australia, European Union, Japan, etc.) and has successfully promoted R and D investments to develop new pharmaceutical products for the treatment of rare diseases.

Figure1.1: orphan drug Disease (rare)

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Committee for Orphan Medicinal Product (COMP) is a committee for EMA which is responsible for providing orphan designation of drugs for rare diseases. COMP is responsible for evaluating the orphan designations. Orphan designation allows pharma industry to take benefit regarding the incentives like (reduced fee, lesser competition in market) from the European Union. [2]

Orphan drug designations approve the sponsors for incentives such as:

I. Clinical trials tax credit(50% of clinical trials costs)
II. Exemption from user fees (over $2 million)
III. 7 years of market exclusivity after the approval process is carried out

60% of the designated orphan is generally intended for pediatric use.
The Pediatric investigation plan provides information for medicines authorization which is provided in product information are eligible for extending of their Supplementary protection certificate.

The US FDA and EMA had jointly collaborated for sharing the orphan medicines information under the confidential agreement. Both this regulatory have a common procedure to apply for orphan designation and for the submission of Annual report for the development of orphan drugs.

Orphan Drug Act

The Orphan Drug Act (ODA) was a response by Congress to the finding that adequate drugs or biologicals were not available for many rare diseases and conditions, such as Huntington's disease, myoclonus, Amyotrophic Lateral Sclerosis (Lou Gehrig's disease), Tourette syndrome, and muscular dystrophy, which affect only a relatively few individuals. The ODA authorizes incentives, such as market exclusivity and funding for clinical research, for the development of products that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions. The Office of Orphan Product Development in the FDA administers the major provisions of the ODA, including the Orphan Products Grants Program.

Orphan Drug Designation

Orphan Drug Designation (ODD) is granted to drug products that are used to treat a rare disease, defined by the Orphan Drug Act of 1983 as having a prevalence of less than 200,000 cases in the United States. If the drug is a vaccine, diagnostic drug, or preventive drug, a rare disease or condition is also defined as having an incidence of less than 200,000 cases/year. Sponsors may also be eligible for designation if they are developing a product for which there is no reasonable expectation for product development costs to be recouped.

As described in 21 CFR 316.20(a), Sponsors may request ODD for a previously unapproved drug, or for a new orphan indication for an approved drug. Sponsors of a drug previously approved as an orphan drug may request ODD for another drug for the same indication if they present a plausible hypothesis that the drug may be clinically superior to the first drug. Multiple Sponsors may receive ODD for one drug for the same indication.

Special Considerations

Pharmaceutical companies are businesses that must cover their expenses and provide a profit to their investors. However, there is great risk involved in developing drugs with few users. If disease drugs were priced to cover the cost of development, most users would not be able to afford them. As a result, the policy to provide incentives was created.

SPONSOR's GUIDE TO AN ORPHAN DRUG DESIGNATION:

Regulation (EC) No 141/2000 of 16 Dec. 1999 has stated that the sponsor can submit application of orphan medicinal products designation to agency during the developmental process. The designation application need to be submitted before application of marketing authorization is submitted.

Pre-clinical and clinical data is required for the submission of orphan designation as an evidence. If the data is not available then it would not be considered as a designated orphan drug by the

COMMITTEE OF ORPHAN MEDICINAL PRODUCT.

Sponsor can appeal an opinion of the COMP. The detail submission need to be sent to agency within 90 days of receipt of opinion by the COMP.

Once the final opinion is made by the COMP, the summary of opinion will be published on website of that agency and the commission result will be generated in the Community register.

The COOMP provides parallel application with the regulatory authorities outside the EUROPEAN Union , specially with United States, Japan for the orphan designation. The process is independent from each other. Sponsor need to hold the mutual concern regarding the orphan designation

DEADLINE FOR SUBMISSION OF ORPHAN DRUG DESIGNATION APPLICATION TO EMA (2022/2023)

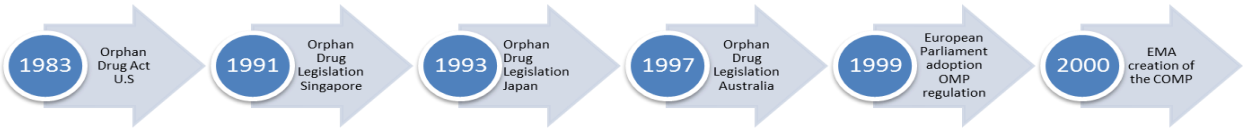
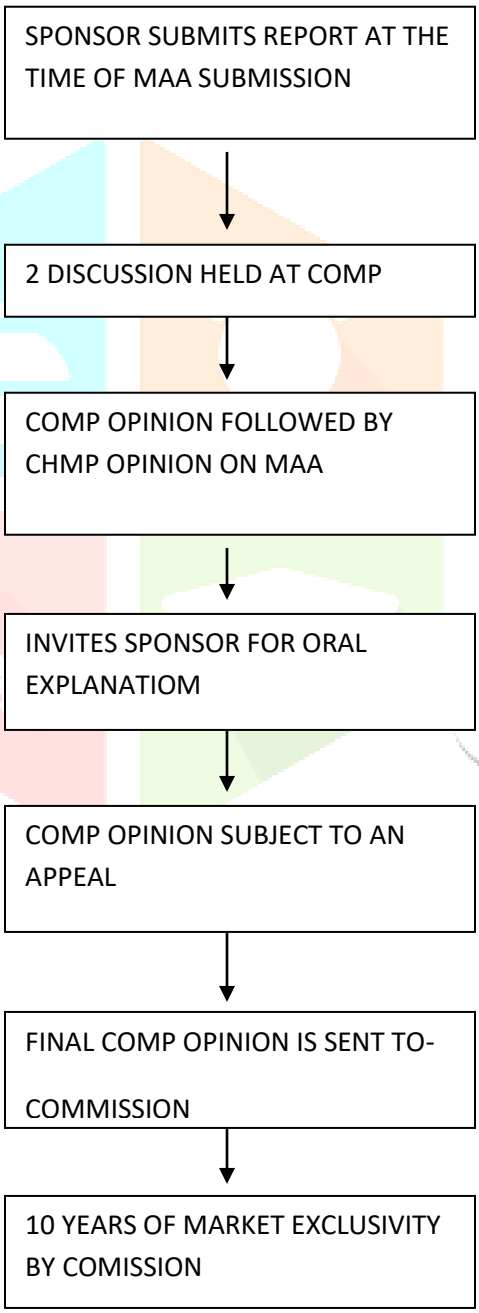


Figure1.2: Orphan Drug Development

PROCEDURE:



ORPHAN DRUG DESIGNATION PROCESS IN UNITED STATES:

- The request for submission of Orphan drug designation can be done by submitting the FDA Form 4035
- FDA will review the request within a 90days period of its receipt.
- Requirements for submission of Form 4035:
- Information about drug product as well as Sponsor.
- Description regarding the rare disease and also the need of therapy for those disease.
- Scientific rationale for using the drug.
- Summary of marketing history and the regulatory status in US
- Documentation stating that the disease meets required qualification for being the rare disease.

APPROVAL PROCESS BY FDA:

Orphan drug designation is a separate process from seeking approval or licensing. Drugs for rare diseases go through the same procedure given below

Figure 1.5: Orphan Drug Approval Process by FDA

COMPARISON OF FDA AND EMA FOR ORPHAN DRUG DESIGNATION:

FDA	EMA
Drugs intended for prevention, diagnosis/ treatment of disease affecting less than 200,000 people in UNITED STATES.	Drug must be intended for life threatening diseases.
	Population affecting must not be more than 5/10,000
Drug will not be profitable within 7yrs. After the approval of FDA.	Drug must be significant to patient having the rare disease condition.

"Orphan Drugs" - Denotation in Various Countries:

- **Japan:** A drug must meet the following three conditions to be considered for orphan drug designation in Japan. Any disease with fewer than 50,000 prevalent cases (0.4%) is Japan's definition of rare. The drug treats a disease or condition for which there are no other treatments available in Japan, or the proposed drug is clinically superior to drugs already available on the Japanese market.

- **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

- **Europe:** A disease or disorder that affects fewer than 5 in 10,000 citizens is the definition for rare in Europe (Orphan Drug Regulation 141/2000). At first glance, this may seem a small number, but by this definition, rare diseases can affect as many as 30 million European Union citizens [3][4][5]

ORPHAN DRUG APPROVAL PROCESS IN CANADA

Current status of ORPHAN drugs in Canada:

The major issue in Canadian Healthcare is the Absence of Canadian Orphan Drug framework. Canadians already has an access to wide range of orphan drugs which are approved in UNITED STATES, because the drugs has been approved for sale/ available in CANADIAN EMERGENCY DRUG RELEASE PROGRAM also known as SAP.

Canada lacks the regulatory functioning which protects orphan drugs.

1. DATA PROTECTION:

It is only available if the manufacture new drug is innovative drug. The previously approved drug with new rare disease cannot be eligible for data protection in Canada.

The US, EU are eligible for previously approved drug with new use in their market for Orphan drug designation.

Manufacturer cannot be eligible for data protection which supports the safety and efficacy of new use or the formulations of Orphan drugs after clinical trials held in Health Canada.

2. PRICE REGULATION ISSUE:

The pricing for patented drugs is overviewed by the Patented Medicines Price Review Board (PMPRB) which affects the orphan drugs as well.

The PMPRB exercises the price control over the drugs which are sold in Canada.

If the price of patented drugs seems to be excess, then the PMPRB can reduce the price of drug based on PATENTED MEDICINES REGULATIONS. Regulations of PMPRB's excess pricing analysis had great impact on the orphan drugs affecting the pharma economic value as well as market size of Canada.

3. STANDARD PATENT DERIVED PROTECTION:

In the Canada, manufacturers can see the protection of orphan drugs same as that of other therapeutic products.

Standard term for patent filling is 20 years from the date of filling of an application. Patent of drugs is eligible to extend for 2 years through CERTIFICATE FOR SUPPLEMENTARY PROTECTION (CSP). [6] [7] [8]

Global orphan drugs market:

The global orphan drugs market size was valued at $1,40,000.0 million in 2020 and is projected to reach $4,35,686.3 million by 2030 registering a CAGR of 11.8% from 2021 to 2030. An orphan drug is a special pharmaceutical agent, designed and developed to treat rare medical conditions.

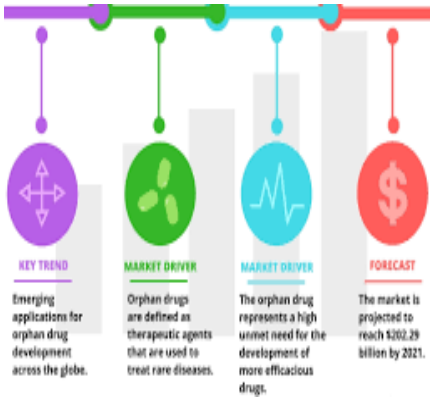


Figure1.4: Global market orphan drug [9][10]

Challenges in orphan drug development

Even as more orphan drugs are developed and approved, almost 95% of known rare diseases have no treatment. Drug development for orphan diseases can be quite challenging. Some obstacles include: little knowledge about the underlying causes and natural history of the disease; difficulty in identifying patients due to low prevalence, which in turn affects clinical trial design; difficulty in diagnosis due to varied symptoms often associated with one condition; and, special consideration for infant patients.[11]

For many, a challenge in the orphan drugs market is cost. The world's most expensive drug, onasemnogene abeparvovec (Zolgensma; Novartis [NOVN: VX]), is a gene replacement therapy treatment for spinal muscular atrophy. It has a price tag of $2.125 million. In the USA, the drug is covered by insurance under strict policies by some payers, or not covered at all. [12] Orphan drugs are quite expensive due to the cost of R&D and the perceived economic non-viability of the products as they serve only a small subset of the population[13] . There is also often a monopoly on orphan drugs for a certain rare disease. Pharmaceutical companies receive seven years of exclusive rights to the marketplace upon approval of their medicine for an orphan disease. This means the FDA will not grant approval to another competitor for the same disease, even after the company's patent has run out.[14]

CONCLUSION:

The orphan drug programs relating to rare diseases have met success only in some countries. In a market where first-mover advantages are small, it is difficult to find the appropriate incentive system.[15] The system created by the ODA has led to an increase in the development, approval, and availability of orphan products. While the market exclusivity provision has expanded access to orphan drugs, it may be erroneously providing exclusive market protection for other products.

Pharmaceutical industries may look forward to invest in such therapies along with researchers. Researchers those who are working on Orphan drugs need to know about the incentives and benefits provided by Non-Government Organizations.

A country should try to produce important drugs for the benefit of the whole world, depending on the R and D investment, the return on such investment, the tax and patent incentives, and its regulatory policies. Agreement of these points might lead to beneficial changes in our national thinking and prevent "orphanisation of new drugs."[16]

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