



## AN INSIGHT ON ORPHAN DRUG DEVELOPMENT STRATEGY IN US AND EUROPE

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### ABSTRACT

More than 25 years of orphan drug regulations have yielded several new treatments for patients with rare diseases. Orphan diseases are typically those that are having no commercial incentives to research and develop actual therapies. To boost the pharmaceutical companies to invest in the development of orphan drug, various countries, beginning with the USA, they have announced their own regulations to provide suitable motivations. There is a significant degree of similarity in the incentives provided from one nation to another and this variety from market exclusivity for the product in its proposed indication (the most important incentive) to tax credits and reduction or waivers of fees. In this article it introduces the orphan drugs and gives legal framework for its regulation in US and Europe. Along with specifications for the Orphan drugs it includes its requirements and features of Fast-track Approval process for quick Marketing authorization.

**Key Words:** Orphan drugs, rare disease, Regulation of Orphan drugs, Orphan medicinal Products, Orphan disease, Fast-track approval process.

### INTRODUCTION

The World Health Organization gives the idea about Orphan or Rare diseases as; it is the pathological conditions that affect 0.65-1 out of every 1000 population. The EU defines a rare disease that affecting 5 peoples out of 10,000 Europeans; The USA accept the condition as a Rare disease as it affecting less than 200,000 peoples or the condition that affects less than 1 out of 5,000 in the general population; Japan has the limit up to 50,000 Japanese patients and Australia accepts the disease as an Orphan disease, that affects less than 1 at 2000 Australian patients. There are approximately 6,000 Orphan diseases, out of which 80% are genetic. In the early 1980's in the US, there is a set-up of the concept of Orphan drug and its regulation. It characterized a young boy suffered from Tourette syndrome, which generated a public opinion for unfortunate victims of these diseases. Due to this issue in the public decision, in 1981 the Orphan Drug Bill was passed.

As Pharmaceutical companies generally invest many millions of dollars to develop single new drug, the interest of companies were diverted towards the development of drugs that are used for the large patient population (Non-Orphan drugs). But due to enforcement of the own legislation regarding the incentives, tax credits and research funds, the companies are now attracted towards the development and marketing of the Orphan medicinal products. For easy and quick approval process for the Orphan designated drugs, the individual countries (US, Europe and Japan) have adopted the Fast-track approval process (As there is decrease in the time up to 0.8 years or 273 days in US).<sup>[1]</sup>

### NEED FOR ORPHAN DRUG REGULATION

Absence of specific treatment for orphan disease causes psychological distress to the patient and the family also, and a feeling of hopelessness. Many diseases having no specific therapy are the most important targets for innovative therapy. The USA became the first country who proposed a legal framework to inspire development and availability of orphan drugs. The Orphan Drug Act (ODA) was came in to force on January 28, 1983, with the main motto to motivate the examination, expansion, and authorisation of new products which mainly focussed on the treatment of rare diseases. Drugs are approved for 'Orphan' status for its precise indication, and still there is

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a need to focus on the studies regarding their safety and efficacy, and after that the product will be qualified for the accelerated approval.<sup>[1]</sup>

## **INCENTIVES FOR INDUSTRY**

- Tax incentives for clinical research,
- Study design assistance from FDA,
- Freedom from fees that are intended for application-filing,
- Grant for Phase I and II clinical trials, and
- Marketing exclusivity of seven years after the approval of the drug or biological product in US and Ten years in EU.
- More than 10 million patients have been treated since the incorporation of Orphan Drug Act, which has stimulated research of orphan diseases. Regulation regarding Orphan drugs exists in various countries like USA, Australia, Japan, Sweden, Singapore, Canada, France, and United Kingdom.
- The US ODA, which is the main base for the initiation of other countries, with variations like marketing exclusivity rights to the marketing company for 7 years in USA, 10 years in Japan, and 5 years in Australia. Countries like South Korea, New Zealand and India establish similar legislation.<sup>[2]</sup>

## **ORPHAN DRUG RESEARCH AND DEVELOPMENT**

### ***Orphan drug research and development by public funding:-***

Apart from industry, a research on rare diseases and drugs for that particular disease is carried out by academic organisations and thus society is now paying twice money for the R&D of the drugs for rare diseases. Indeed, this view is also frequently expressed about drug research and development in general. However, these researchers focus on noticing the new scientific facts and exploring a totally new opportunities, not only on making products. Once biomedical research becomes more translational. For example, recognizing the suitable drug candidates and conducting clinical trials that are nearly completely followed by the sponsors. The translational steps in the development of new emerging drugs request high numbers of standards for the control of quality and reproducibility, which contains large amounts of money investment and there is a need for well trained personnel. In addition to these, most clinical trials, even for very small patient inhabitants, it can be more costly. Highly controlled and regulated manufacturing processes are

essential to provide a safe and efficient final product that reliably achieves the regulatory marketing authorization requirements.<sup>[2]</sup>

### ***Relative costs and regulation of orphan drug development:-***

A common misreading is that orphan drugs are inexpensive to develop than other drugs because lesser clinical trials are essential and they are focus to different regulatory standards. Researching, developing, manufacturing and bringing to market any drug is a lengthy, difficult process and latest statistics suggest that about 30% of all drugs still fail in Phase III trials, while others notify that this quantity could be as high as 50%. With regard to orphan drugs, every single stage of the development method is further complicated by disease rarity.<sup>[2]</sup>

## **US**

### **THE USA ORPHAN DRUG ACT**

The U.S. Orphan Drug Act was signed into law in 1983 and for the first time, that provided special incentives for the pharmaceutical companies to develop drugs that had minimal commercial return on the investment, but which are essential and life-saving for patients with Orphan diseases. The Orphan Drug Act is introduced in 21 CFR Part 316. From 1983 to the end of 2005, 1463 drugs received orphan drug designation. Of those, 289 drugs have received marketing approval and approximately 14 million patients treated annually. It is estimated that one new orphan drug saves approximately 211 lives per year. The Office of Orphan Products Development (OOPD) was created within the Office of the Commissioner with mainly 2 objectives:-

- To evaluate requests for orphan drug designation
- To evaluate, award, and monitor the progress of orphan drug grants.

This OOPD act as an internal FDA advocate to interface with the FDA review division to help and facilitate the progress. It is mainly responsible for evaluating data in terms of risk-versus-benefit considerations.<sup>[3]</sup>

### **REGULATORY TIMELINE**

In 1983, U. S. orphan drug act was taken place. In 1984, there is a change in the existing definition of "rare disease or condition" as any disease or condition that affects less than 2, 00,000 persons in the United States. In 1985 there is an amendment regarding extension of the marketing exclusivity to patentable as well as non-patentable drugs and allowed for grants for the clinical evaluation of orphan designated drugs. The 1988 amendment concentrates on industry sponsors to apply for orphan designation prior to submission of a

marketing application for marketing approval. In 1992, The Orphan Drug complete legislation was published in the *Federal Register* on December 29, 1992, and became effective 30 days later. In The FDA Modernization Act of 1997, there is an exemption for designation of orphan drug products from paying new drug application fees (\$774,000 in 2006).<sup>[3]</sup>

### FAST-TRACK APPROVAL PROCESS

After the thalidomide tragedy, it was realized that the more severe phase is phase II and III clinical trials, and they were required prior to approval for marketing authorization of a drug. But in contemporary times, the situation has changed. The AIDS crisis has stimulated a strike back from the expensive and rigorous pre-marketing review, to more fast track processes, with the intention of getting relief from fast spreading and fatal diseases. Fast-track designation does not apply to a drug alone, but it applies to the combination of an innovator drug, and certain indication being studied. Drugs that are anticipated to treat a severe condition must be therapeutic (treat a serious manifestation or symptom), diagnostic (improve detection or diagnosis), preventive (prevent serious consequences), or nonexistence of the serious adverse effects.<sup>[3]</sup>

For fast-track designation, one of the two conditions must be met,

1. No therapy must exist for that specific condition,
2. The new therapy must demonstrate a better effect along with enhanced alternative outcomes other than the current therapy, avoid severe toxicities accompanying with existing therapy, or proposed developed compliance and convenience compared to current therapy.

There are mainly 4 types of approval process for the Orphan designated drugs,

1. Fast-track
2. Breakthrough therapy
3. Accelerated approval
4. Priority review

#### (1) Fast-track:

A drug that is intended to treat a serious condition AND nonclinical or clinical data demonstrate the potential to address unmet medical need OR A drug that has been designated as a qualified infectious disease product. Features of Fast Track Designation are to accelerate Development and Review. Qualifying Norms for Fast Track Designation,

- Serious Condition

- Representing the Probable Unmet Medical Need

#### (2) Breakthrough therapy:

This process is for the drug which is intended, alone or in combination with 1 or more other drugs; to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.

Qualifying Norms for Breakthrough Therapy Designation,

- Serious Condition
- Existing (or Available) Therapies
- Preliminary Clinical Evidence

#### (3) Accelerated approval:

It is made available to a product for a serious or life-threatening disease or condition upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.

Qualifying Norms for Accelerated Approval,

- Serious Condition
- Expressive Benefits Over Existing Therapy

#### (4) Priority review:

An application for a drug will receive priority review designation if it is for a drug that treats a serious illness and, if permitted, it would make available a significant improvement in safety or efficacy. A priority designation is anticipated to direct overall attention and resources to the evaluation of such applications. Qualifying Norms for Priority Review Designation,

- Serious condition
- Representing the prospective to be a significant improvement in safety or effectiveness.<sup>[3]</sup>

### ORPHAN GRANT PROGRAM

FDA generally allocate \$14 million grant for Orphan drug annually. They allot 10-15 new grants for drugs per year.

On-going clinical trials at any phase are eligible to get a grant for the Orphan designation.

#### Conditions:

- The clinical trial must be conducted under active U. S. IND.
- Phase-I is eligible for \$200,000 per year for up to 3 years.
- Phase-II & III is qualified for \$400,000 per year for up to 4 years.<sup>[4]</sup>

### **US ORPHAN DRUGS STATUS**

- More than 400 approved Orphan drugs
- About 2000 designated Orphan medicinal products.<sup>[5]</sup>

### **EUROPE**

#### **INTRODUCTION**

In the European Union, there are usually 2 parts of orphan drug legislation – both of which are Regulations and, therefore, directly applicable in all Member States.

The first is the Regulation (EC) No 141/2000, which is deals with

- The definitions
- Purpose
- Criteria for designation
- The procedures and provision of protocol assistance which includes scientific advice
- Establishment the Committee for Orphan Medicinal Products (COMP), to perform centralized procedure

The second one is the Commission Regulation (EC) No 847/2000, which includes,

- The requirements for employment of the criteria for designation
- The concepts of ‘similar medicinal product’ and ‘clinical superiority’

After this regulation, the European Commission wants to implement the designation and market exclusivity provisions to provide guidance to the European Medicines Evaluation Agency, the Member States and the pharmaceutical industry. The purpose of this regulation is to provide procedure for the designation of the Orphan drug products and to provide incentives for the research, development and for placed it in the arcade of designated orphan medicinal products. They include certain criteria for drugs to come under the “Orphan Status”.

- Population affected from that particular disease should be less than 5 persons out of 10,000 peoples.
- Condition of that disease should be life-threatening.
- No any other method should be there in the market to treat that disease condition or this new drug should be more significant than the existing methods or drugs.

As between 6,000 – 8,000 rare diseases exist in the world, the population that are affected is approximately in total 27 to 36 million people in the EU and it is approximately 6-8% of the total European Union population. Rendering to this legislation, rare disease is the condition that affects less than 5 people out of 10,000 peoples. There is a use of Centralized procedure for the European Union. The application should be short as much as 30 pages. And if the same invention is applied for additional one indication, then separate applications should be submitted for each orphan indication. In this concern, ‘treatment’ and ‘prevention’ of the same condition are considered as two separate indications and should be the subject of two separate applications. A sponsor shall submit to the EMA an electronic version of the complete application for designation including full bibliographical references to [orphandrugs@ema.europa.eu](mailto:orphandrugs@ema.europa.eu).<sup>[6]</sup>

#### **TIMELINE**

- August 1996 – First draft the Regulation (EC) No 141/2000 and (EC) No 847/2000
- December 1999 –Acceptance of the regulation
- June 2000 –First application filed for the Orphan drug is validated by the Committee for Orphan Medicinal Products (COMP)
- July 2000 – Submission of first Marketing Authorization Application (MAA)
- August 2001 – For the Orphan drug there is a first approval
- March 2002 – Public opinion summary is conducted
- April 2009 –First time more than 100 positive opinions
- Up to 2014 – 100<sup>th</sup> marketing authorization for Orphan drug products<sup>[6]</sup>

#### **INCENTIVES**

Marketing Exclusivity: 10 years (6 years if product is highly profitable)

Fee reduction:

- 75% fee reduction (100% for SMEs) on Protocol assistance, initial and follow-up requests,

- 100% for paediatric-related assistance
- 10% fee reduction on Marketing Authorisation Application
- 100% fee reduction for Inspections (pre-authorisation)

Tax reduction & Research grants: It is made available in some member states <sup>[6]</sup>

## PARTS OF REGULATION

- A. Regulation (EC) No 141/2000:
- Designation Route for Orphan medicinal products
  - Provide framework for the incentives for the development and the marketing of the designated Orphan medicinal products
  - Establish the Committee of Orphan Medicinal Products (COMP)
- B. Regulation (EC) No 847/2000:
- It includes some definitions that are essential for the designation of the Orphan drugs by implementing the above regulation
- C. European Commission Communication 2003/C 178/02:
- Provision for Market Exclusivity
- D. Regulation (EC) No 726/2004:
- Provides the framework to the Centralised procedure for the Marketing Authorization in the European Union
- E. Regulation (EC) No 507/2006:
- Give the lay-out for the Conditional marketing authorization for the Orphan medicinal products that falls within the regulation
- F. Regulation (EC) No 1901/2006:
- It provides the legal regulation for the marketing authorization for the Paediatric Orphan drugs
- G. Regulation (EC) No 2049/2005:
- It is regarding the payment of fees
  - Provide the Scientific advice and review to that Orphan drug <sup>[6]</sup>

### TRANSFER OF THE ORPHAN DESIGNATION STATUS TO ANOTHER SPONSOR

- A. Transfer of the Orphan designation to another sponsor: The sponsor of the orphan drugs should submit an application in electronic format to the EMA. Documents that are needed for this are as per below:
- Name and address of the sponsor who is originally holder of that and the sponsor to whom designation is to be transferred

- Proof shows that the sponsor to whom the designation is to be transferred is established in the Union
- A document that certifies that a comprehensive and up-to-date designation application has been transferred to the person to whom the transfer is to be granted

B. Change in the name of the Sponsor and/or the address of the Sponsor: Here sponsor remains same before and after the application. Documents that are needed for this are as per below:

- Signed letter of the application is submitted to the European Commission in the electronic format
- The letter should clearly specify the new name and/or address details with its state
- A copy of the certificate for the modification in name should be attached to the letter
- In the case of a name change, the identity of the firm remains same as it before<sup>[7]</sup>

## FAST-TRACK APPROVAL PROCESS

On 18 July 2001 the European Directive suggested a fast track approval procedure for the European Agency for Evaluation of Medicinal Products (EMA), in response to the delayed market access experienced by drug approval applicants in the EU.

### Requirements:

- The condition being life threatening or serious;
- There should be no effective therapeutic substitute; and
- The drug being expected to have a high therapeutic benefit <sup>[6]</sup>

## EU ORPHAN DRUGS STATUS

- 1454 applications submitted
- 1021 designations having positive COMP opinion
- 989 designations granted by European Commission
- 18 final negative opinions (1%)
- 360 applications withdrawn (26%) <sup>[6]</sup>

## ADVANTAGES OF ORPHAN DRUG DEVELOPMENT

As of February 2011, there were 460 medicines to treat or prevent rare disease under clinical trials in the US alone. Developmental drivers such as government incentives, shorter development timelines and high rates of regulatory approval are making orphan drug

development as economically viable as non-orphan drug development, even though the patient pool is smaller. The time from Phase II to market is often shorter for orphan drugs due to shorter and smaller clinical trials and FDA Fast Track designation. The average period since Phase II to launch was 3.9 years for orphan drugs, while for non-orphan drugs time taken is 5.4 years. Once a compound has been granted for orphan designation, the probabilities for authorization are great (82%) related to traditional drugs (35%). Of note, orphan designation for the drug in the orphan indication is maintained regardless of subsequent indications. As an outcome, one classic model for expansion is based on lead development of a compound with a relatively quick-to-market orphan indication, followed by deliberation of expansion to other indications. The revenue creating ability of orphan drugs is compounded in cases where drugs have multiple orphan disease indications, or go on to gain approval for larger, non-orphan disease indications. In addition, a high number of orphan drugs are of the category from biologics, having less generic equivalents, prolonging their importance to sponsors, even after the ending of patent term. [2]

## CONCLUSION

In the past several years, orphan drug legislation, started in the United States and improved by a host of coordinated health policy actions in the European Union, have augmented curiosity in orphan diseases as a health priority and have a sharp increase in orphan drug development. But, it is anticipated that only ~10% of rare diseases have an available treatment and such treatments can often still be improved. Looking at the current orphan drug regulation strategy, it has allocated with the regulatory features of the development and the approval of orphan medicinal products, and the economic benefits for such development. The arrangement of research, or disputes associated to analysis and access, are not covered by such protocols. With a growing figure of orphan medicinal products available, these aspects are gaining in reputation. It would be valuable to also develop incentives for the repurposing of medicines that are already approved for a more common disease into a new rare disease indication. In this respect, the first aspect that needs attention is the documentation of off label use of both orphan drugs and drugs approved for common diseases for a rare disease indication. Due to this outline, it will become clearer that which drugs will be worth developing for such new indications and what incentives are needed. At the global level, increased

international regulatory and health policy collaborations and exchange of information would avoid duplicate work and ensure the best use of Orphan disease knowledge which would also permit the cost savings for sponsors and authorities to provide prior delivery of the specific Orphan drugs to the patients suffered from particular rare disease conditions. The United States and the European Union should take the lead in sharing their experience and expertise further than they are today.

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