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Navigating through orphan medicinal product regulations in EU and US – Similarities and differences

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ABSTRACT

Rare diseases as the name suggests are the diseases which occur in a very small population due to which the development of medicinal products for these diseases is sidelined as it is anticipated that the cost of development will never be recovered from the sales. It has been estimated by National Institute of Health (NIH) that globally around 7000 rare diseases are there, many of which are of genetic origin. This paper aims to analyze the basic similarities and differences between the rules and regulations put forth by regulatory agencies of US and EU for development of medicinal products for rare diseases, also called orphan medicinal products. The basic purpose was to carve out the loopholes as well as positive aspects of each of these acts and regulations so as to have a clear understanding on the subject. It was to understand that how these legal instruments have stimulated the growth of the drug products for rare diseases and what other things can be done in order to achieve a better impact. This article also provides an overview of the various incentives offered as well as challenges and hurdles faced by each of these regulatory agencies while implementing these regulations.

1. Introduction

The total number of patients in Europe and US suffering from a rare disease is estimated to be 55 million (Stolk et al., 2006; Schieppati et al., 2008) and hence as such rare disorders are considered a critical problem. From the investment point of view the medicines for these diseases are not thought of as very good options and consequently the number of medicines available in market is quite less. Another reason for less number of medicinal products for rare diseases is very limited number of patients and inadequate knowledge for carrying out research. As has been appropriately mentioned that "patients with rare diseases have the same right to treatment as patients with more prevalent diseases, ways are required to stimulate the pharmaceutical as well as biotechnological industries to develop such products" (Biotech fact sheet, Europa Bio, Rare Diseases and Orphan medicinal products, October 2002).

Before various regulations concerning orphan drug products came into effect, there were reasons to believe that drugs for some of these rare diseases would not be developed unless there are some measures adopted by the regulatory agencies to reduce the cost of development of these drugs and also make some changes in the prevailing acts and regulations.

Hence with a view to encourage the development of medicines for rare diseases, various regulatory agencies all across the globe namely EMA, FDA, Japan regulatory agency (MHLW), Australian agency started introducing various regulations and acts for promoting development of these medicinal products and also including some additional benefits and rewards as a result of development. There are various similarities and differences between these regulations which have been put in place by 2 major regulatory agencies i.e. EMA and US FDA and there is a need of comparison of the procedures followed by both the agencies.

In addition to this, the discussion on various negative and positive factors of the acts and regulations followed by both agencies would also help in better understanding of the process.

2. Discussion

2.1. Orphan Drug Act – US

United States regulatory authority was much ahead of EMA in recognizing the need for a legislation concerning the development of medicinal products for rare diseases. In United States, several

Abbreviations: CFR, Code of Federal Regulations; CHMP, Committee for Medicinal Products for Human Use; COMP, Committee for Orphan Medicinal Products; EC, European Commission; EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration; MHLW, Ministry of Health, Labour and Welfare; NIH, National Institute of Health; NORD, National Organization for Rare Disorders; OOPD, Office of Orphan Products Development; ODA, Orphan Drug Act.

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of the rare disease patient organizations joined together in a coalition to solve the orphan drug problem and this group was known as orphan drug coalition which later became the National Organization for Rare Disorders after the Orphan Drug Act became law in 1983 (Meyers, 2000).

Orphan Drug Act was first passed on 4th January 1983 by FDA after which many amendments have been subsequently passed till date. The latest one is the orphan drug regulation final rule, June 12, 2013 effective from August 12, 2013 which has further resulted in clarity on regulatory language used as well as minor areas of improvement regarding orphan drug designation and approvals. The Orphan Drug Act before granting orphan drug designation to a product takes into consideration the prevalence of disease for which it is indicated in the US population. The FDA's Office of Orphan Products Development, OOPD was also set up to encourage the development of drug products, biological products, medical devices and dietary supplements for rare conditions by offering financial incentives to product sponsors.

As per ODA, the term "rare disease or condition" means any disease or condition which:

(a) Affects less than 200,000 persons in the United States, or
(b) Affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will recovered from sales in the United States of such drug. Determinations under the preceding sentence with respect to any drug shall be made on the basis of the facts and circumstances as of the date the request for designation of the drug under this subsection is made (21 CFR, 2013).

The basic process of bringing an orphan drug product into market has been streamlined as per this act and starts with the request for written recommendation for expected nonclinical and clinical studies on the product. The next step is to obtain the orphan drug designation for which a certain amount of data needs to be submitted to the FDA. A sponsor can at any point of time during the development of the drug submit a request for orphan drug designation. The orphan drug designation may be requested for an unapproved or of a new use of already marketed drug. In addition to this it is also possible to apply for the orphan drug designation for another drug for same rare disease or condition if the sponsor can present a plausible hypothesis that the drug is clinically superior to the previously approved drug (21 CFR, 2013). More than one sponsor can receive the orphan drug designation for the same drug for same condition but market exclusivity will be provided to the one who receives the approval to market the drug first.

As per Part 316 of 21 CFR on receipt of the request FDA verifies that the conditions of the orphan drug are fulfilled and all the necessary studies and justifications have been provided in the application. In case of deficiency in the application FDA may ask the applicant or the sponsor for which a maximum timeline of 1 year of issuance of deficiency letter has been provided unless a request for extension has been asked for by the sponsor. The FDA based upon its review may then grant orphan drug designation or refuse to grant the designation.

After a drug product has been designated as orphan, annual reports including in brief the progress of drug development, future plans and changes if any after the designation should be submitted within the 14 months of the after the drug was designated as an orphan drug and annually thereafter till marketing approval has been sought.

In certain circumstances FDA may approve another sponsor for the same and alternative orphan drug for the same indication if any of the following conditions are met:

- Withdrawal of exclusive approval or revocation of orphan-drug designation by FDA under any provision of this part; or
- Withdrawal for any reason of the marketing application for the drug in question; or
- Consent by the holder of exclusive approval to permit another marketing application to gain approval; or
- Failure of the holder of exclusive approval to assure a sufficient quantity of the drug.

When a request for orphan-drug designation is granted, FDA will notify the sponsor in writing and will publicize the orphan-drug designation which is updated every month.

There is also a provision to apply for amendments at any time prior to marketing application approval for any changes due to justified reasons and also transfer the ownership of the orphan drug to another sponsor after receipt of designation.

In US, various expedited development and review programs are also available so as to facilitate and expedite the development and review of new drugs products that are used in the treatment of serious or life threatening conditions and have proven to be having some exceptional characteristics. These programs include fast track designation, accelerated approval, priority review, and breakthrough therapy designation. In May 2014, US FDA issued guidance for industry (Expedited programs, 2014) on the policies and procedures applicable for concluding a drug as a potential candidate for these programs. Orphan medicinal products which fulfill the conditions described in this guidance may further benefit through one of these procedures during development and or review process.

2.2. Orphan drug regulation EC/141/2000 – EU

In EU the regulation concerning drug products for rare disease was implemented much later than in US and it was aimed to encourage the industry to develop and market medicinal products for rare diseases. Almost 20 years after US, on 16 December 1999, the European Parliament and the Council adopted regulation (EC) No 141/2000 on orphan drugs. Additionally regulation (EC) No 847/2000 of 27 April 2000 was also adopted by EC which established the application procedures for orphan designation as well as introduced the concepts of clinical superiority and similar medicinal products. In compliance with Article 4 of Regulation (EC) No 141/2000, a separate Committee for Orphan Medicinal Products within the agency was also set up.

The main roles of the committee were to assess the applications for designation of orphan medicinal products, to assist in framing the policies, procedures and guidelines related to orphan medicinal products and also assist in liasoning of the agency internationally on matters related to orphan medicinal products.

As per EU, rare diseases are life-threatening or chronically debilitating conditions affecting no more than 5 in 10,000 people in the EU and it has been observed that mostly these diseases affect less than 1 in 100,000 people.

A product can be designated as an orphan medicinal product in EU, if certain conditions are satisfied and these are (Regulation (EC) No 141/2000, 2000):

- it must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating;
- the prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development;
- no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorized, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.