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A REVIEW ON ORPHAN DRUGS- INDIAN PERSPECTIVE

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ABSTRACT

WHO defines rare disease as a disease or condition with a prevalence of ≤1/1000 population. Other definitions are diseases affecting <1/2000 population in European union, whereas USFDA defines it as any disorder affecting <200,000 population at a single time point. Ultra rare disease is a disease affecting <2 patients/100,000population. However, rare diseases are indeed not so rare. As most of definitions are based on the prevalence of disease, the orphan disease burden is high in countries with high population. A disease can be rare in a region but may be very common in another region, for example, IgA nephropathy is common in Asia and Africa, but rare in European Union. Lots of issues complicate the drug development process of rare diseases, for example, less understood pathophysiology, lack of validated preclinical models, less research, and lack of standard comparator drug. Clinical issues such as lack of information about natural history of the disease, poorly defined endpoints, poor trial design and inadequate sample size, recruitment problems, lack of well-defined diagnostic criteria, and other issues such as nonexistent comparator drug and funding problems. Although multicentric trials can short out this issue, it has own drawback such as lack of consistency in diagnostic facility in small centers and regional sociocultural variation. Like other drug development, orphan drug developmental is also a costly process. Industries show negligible interest in the development of treatment for rare diseases as there is less return on investment. Mostly, orphan drug research is dependent on government incentives. USFDA, EMEA, Japan, and many other countries offer benefits such as protocol assistance, fast-tract approval, waiver of fees, and marketing exclusivity. In

this context, here, we are going to deliberate the different initiatives to accelerate the development of orphan disease research in India.

KEYWORDS: Orphan Drugs, Orphan Diseases.

1. INTRODUCTION

ORPHAN DRUG

Any drug is developed to treat an "Orphan or Rare diseases" condition is called an Orphan drug. These are not developed by the pharmaceutical industry for economic reasons but which respond to public health need. Developing a Orphan drug is extremely challenging for any pharmaceutical company because of High cost intensive R&D initiatives and Availability of a low return on investments.

ORPHAN DISEASES

Neglected diseases: Rare diseases and tropical diseases. Any disease that affects a small percentage of the population. About 250 new rare diseases are discovered each year. Medical literatures describe about 7000 rare diseases; in that 650 have received official designation as rare diseases(Europe)

The known rare diseases include
Autoimmune diseases, Cancer types, Communication disorders, Cutaneous Conditions, Endocrine diseases, Eye diseases and disorders, Genetic disorders(80%), Intestinal diseases, Neurological disorders.

A medicinal product designated as an orphan drug is one that has been developed specifically to treat a rare medical condition referred to as "orphan disease." It may be defined as drugs that are not developed by the pharmaceutical industry for economic reasons but which respond to public health need.[1] The spiralling 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.[1]

Orphan drugs are an important public health issue and a challenge for the medical community.[2] Modern society still has a lack of options for the effective treatment of patients with rare diseases. As one of the consequences of this, the demand for public health protection has increased the economic burden of a patient suffering from such diseases.[3] Scientific advances have given researchers a new tool to explore these orphan diseases, which are often more complex than common diseases. On the brighter side, these rare diseases when taken together cannot be called rare at all. There are approximately 7000 different types of rare diseases and disorders with more being discovered today. It has been reported that there are about 250 new rare cases reported every year, however, the acceptable treatment is available only for 200-300 orphan diseases.[4] It is known that the 80% of these rare diseases are of genetic origin and the rest have environmental, bacterial, viral or unknown origin [4]. Overall orphan diseases are often chronic, progressive, disabling; even life-threatening and most of these have effective or curative treatment, having low prevalence and high complexity.[5]

Evolution of Orphan Drug Act (ODA): The regulations resulting from the FD and C Act and the 1962 Amendment had especially negative consequences for orphan drugs. Because orphan drugs target small populations and yield lower returns, Asbury (1992) finds only four drugs that were on the market to treat rare diseases by 1965. Legislation significantly increased the costs associated with drug development and caused pharmaceutical companies to focus their attention on drugs that would maximize profits and the possibility of recouping their R and D costs.

Many people considered rare diseases to be “orphaned” or essentially ignored by drug manufacturers, due to the focus on profitable “blockbuster” treatments, defined as drugs that are expected to generate over $1 billion in sales annually. Because of their neglect, these treatments earned the label “orphan drug.” Eventually, the influence of non-governmental organizations, like the National Organization for Rare Disorders (NORD) and patient advocacy groups, made orphan drug development a focus of public policy in the late 1970s and early 1980s. In 1980 Congress implemented the Bayh-Dole Act (PL No. 96-517, 1984), allowing the recipients of government-sponsored R and D to patent and licensed their research, followed by the Orphan Drug Act in 1983.[6]

The Orphan Drug Act (ODA) of 1983: Before the Orphan Drug Act (ODA) of 1983, the FDA had approved only 58 orphan designations, with fewer than 10 approved in the decade

before the ODA was passed (Pharma, 2013). After the ODA, existing drugs that qualified had to be reapproved to gain market exclusivity and the benefits of the Act. The ODA has several parts, but its main purpose is to reduce costs and increase the returns to orphan drug production. Additionally, the ODA allows the FDA to expedite orphan drug designation approvals over other drugs, reducing the development time.[7] In 1997 Congress made a 50% tax credit on R and D expenditures a permanent feature of the Act. This credit goes towards clinical trial expenses of drugs that have received official orphan drug status by the FDA.[6] The most contested provision of the ODA is the seven years of market exclusivity rights that pharmaceutical companies can obtain for orphan products, which grants them a monopoly over the marketing of the drug for a particular indication.

Since the act has been enacted, it has been amended for numerous times by Congress. Initially, orphan status was only granted to drug manufacturers that demonstrated that the development of an orphan drug would be unprofitable and the costs would not be recouped through US sales. Orphan drugs could be profitable through worldwide sales as long as there were no "reasonable expectation" that US sales would exceed the development costs. Orphan drug exclusivity status was restricted to drugs that could not be patented, as some biotech drugs had difficulty in obtaining patents.

However, in 1985 another amendment to the ODA dropped that restriction. In reality, most orphan products could obtain patents, but it was because of the lengthy approval process that many of the patents expired before the product was able to reach the market, making them redundant. In 1990 Congress passed a proposal to limit market exclusivity, but President George H. W. Bush vetoed the amendment. Most recently, the FDA amended the ODA on June 12, 2013, to "clarify, streamline, and improve the orphan drug designation process".[8]

2. STATUS OF ORPHAN DISEASE RESEARCH IN INDIA[9-15]

Coming to the Indian scenario, so far, ~450 rare diseases have been identified in India. It was statistically estimated that, in India, the rare disease and disorder population was 72,611,605 as per published data of national population census of 2011. Now, the awareness for rare disease is increasing.[9,10] Scenarios for many rare diseases are also changing. Cystic fibrosis was thought to be very rare in India, but genetic analysis has now shown that the disease is prevalent but was undiagnosed earlier. India has reportedly higher rare diseases population than the world average, but initiatives from government side are still less, and in fact, India

lacks national legislation for orphan medicines and rare diseases, in spite that these are most populated countries.[11,12]

Time to time scientific and patient communities expressed the needs for government initiatives toward rare disease. The first attempt to bring together all experts of rare disease under a common platform was initiated by INSA, which conducted the first of the kind rare disease workshop entitled "To Develop a Scientific Program for Research on Rare Diseases" in 2016, which deliberated on issues such as definition of "Rare disease," rare disease awareness, rare disease research avenues, policy framework for boosting and incentivizing research and development (R and D) efforts, and framing suitable legislation to ensure involvement of the State in fulfilling the special needs of rare diseases. In the INSA rare disease workshop (2016), the honorable drug controller general of India stated that a policy for accelerated clearance of orphan drugs and fast-track approval is not in place because government needs clear-cut recommendations regarding the definition of rare disease, mechanism for fast-track approval (e.g., waiver of a specific phase in orphan drug clinical trial). He again stated that genetic differences in Indian population warrants Indian-centered studies, rather than using data from studies in other countries. He also invited for expert suggestions on the need of changes in the drugs and cosmetic act to meet the requirements of research in rare disease.[13]

Dr. APJ Abdul Kalam addressing the issues of rare disease said, "a coordinated effort at the national level is the need of the hour for more research and understanding rare diseases in the country. There is a need for a whole ecosystem consisting of doctors, a registry to record the prevalence of rare diseases, biobanks, support groups, more research on drug discovery, and of course, a regulatory framework. Each component is complex, and there is a lot of work ahead.[14]

Recently, mobility is seen in terms of rare disease research in India. Different initiatives are in process which includes initiative from regulatory side, initiatives from academic institutes, nongovernmental organization, and other related sectors.

3. CDSCO INITIATIVE[16-22]

By a circular 12-01/14-DC pt. 47 dated July 3, 2014, the CDSCO issued a notice regarding waiver of clinical trial for approval of new drug in the Indian population, for drugs which are already approved outside India, and it was mentioned that this waiver can only be possible in

case of orphan drugs for rare disease and drugs indicated for diseases and condition where there is no therapy.[15]

In another meeting at a later date between pharma stakeholders and DCG(I), held on May 4, 2016, on exploring of possibilities to provide cheaper medicines for patients with rare diseases, IDMA and OPPI were given the responsibility to formulate the Indian definition of rare disease, JDC (ER) was given the responsibility to revise timelines for orphan drug approvals, and a separate cell was suggested to address the issues of rare diseases, possibility of separate pricing mechanism for orphan drugs, and possibility of custom duty exemption.[16]

Pharmaceutical export promotion council initiative

Pharmaceutical export promotion council, Ministry of commerce and industry, India, conducts regular seminars, awareness campaigns regarding quality compliance and orphan drugs, quality culture in good manufacturing practice (GMP) compliance overseas marketing strategies, opportunities for orphan drugs, IPR and interaction with Food and Drug Administration (FDA) of other countries, etc., and takes care of orphan drug export and other related strategy such as GMP compliance, awareness, and strategy maker in collaboration with FDA of other countries.[17]

Uttar Pradesh Government initiative

Incidence of hemophilia incidence in India is estimated to be 1 in 5,000. However, for treatment purpose, clotting factors used are very costly. In the year 2010, the Uttar Pradesh Government took an initiative to cover the cost of clotting factor.[18]

ICMR initiative

Till now, two main initiatives initiated by ICMR are inviting projects for orphan disease research and initiation of registry for rare disease and sponsoring/organizing workshops/conferences/training programs on rare disease. The National Initiative for Rare Diseases (NIRD) was organized jointly by ICMR, AIIMS, JNU, and PRESIDE. It was decided that first step is to identify patients with rare disease. “Indian rare disease registry” was launched on April 27, 2017. This registry is intended to cover all rare and ultrarare diseases prevalent in India. The registry is first intended to be hospital based and later population based. The objectives of the registry are identification of the rare disease patients; use that data for policy framing and to guide future research.[18] Other major benefits are that

monitoring prevalence, incidence, and natural history of disease will become easy with regard to the Indian context.[19]

Nongovernmental organization initiative

Organization for Rare Diseases India (ORDI; www.ordindia.org) is a nonprofit-based voluntarily organization which was established to deal with the rare disease condition in the Indian population. The ORDI team members belong to different disciplines that are science and nonscience background. ORDI deals with the matters related to the rare disease ssuch as unique challenges in dealing with rare disease.[20]

CSIR and IGIB initiative

IGIB, New Delhi, has conducted project funded by CSIR, named as "Genomics for Understanding Rare Diseases India Alliance Network (GUaRDIAN)," for the purpose to bring together and understand novel genetic variations to achieve translational applications by both clinicians and basic science researchers.[21]

JUDICIARY initiative

In November 2016, the Delhi high court had ordered the government to finalize a policy on rare disease, draft of which was submitted by the Union Ministry of Health to the Delhi high court on May 25. The Delhi high court directed the Centre to implement its National Policy for Treatment of Rare Diseases without delay.[22,23]

Academic institutes

Different projects are running with regard to different rare diseases in different institutes such as AIIMS, PGIMER Chandigarh, CMC Vellore, and SGPGI Lucknow.

4. CONCLUSION

As India is still in developing phase, there is setback in regard to regulation and development in orphan diseases research. In the present scenario, there is a strong need in the assessment of the spectrum and burden of orphan diseases and awareness program in mass regarding orphan disease. Strong policies and initiatives are needed from government and private institution for orphan drug development.

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