Orphan drugs: Indian perspective

WHO defines rare disease as a disease or condition with a prevalence of \(\leq 1/1000\) population.\(^{[1]}\) 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.\(^{[2]}\) Ultra rare disease is a disease affecting \(<2\) patients/100,000 population.\(^{[3]}\) 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.\(^{[4]}\) 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.\(^{[5]}\) 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.\(^{[6-9]}\) In this context, here, we are going to deliberate the different initiatives to accelerate the development of orphan disease research in India.

**Status of Orphan Disease Research in India**

Coming to the Indian scenario, so far, \(~450\) rare diseases have been identified in India.\(^{[10]}\) 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.\(^{[11]}\) Now, the awareness for rare disease is increasing.\(^{[10]}\) 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.\(^{[10]}\) India has reportedly higher rare diseases population than the world average, but initiatives from government side are still less\(^{[12]}\) and in fact, India lacks national legislation for orphan medicines and rare diseases, in spite that these are most populated countries.\(^{[13]}\)

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.\(^{[10]}\) 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 clearcut 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.\(^{[10]}\)

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.
CDSCO Initiative

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.[13]

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.[14]

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.[15]

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.[10]

ICMR initiative

Till now, two main initiatives initiated by ICMR are inviting projects for orphan drug 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 such 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.[10]

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.[21-23]

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.

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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