Review Article

Advances in orphan drug development: Time to change the status and stereotype

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Abstract

Rare diseases remain a challenge for many of the countries in the world. The millions of people collectively suffering from rare diseases, in the context of raging COVID-19 pandemics globally, require an innovative and recent solution from different stakeholders. Regulatory bodies such as the Food and Drug Administration and the European Medicines Agency have come up with many different approaches including financial assistance to prompt drug development and approval. Novel approaches pertinent to clinical trials of such drugs such as patient centricity, early interaction with regulatory bodies, and establishing clinical outcome of interest have been experimented. Various international organizations including cross-country collaborators have initiated various projects or consortiums to bridge the gap between knowledge and practice. The challenges remain more pivotal in developing countries such as India, which has adopted few noteworthy initiatives by involving relevant stakeholders in the presence of limited resources, infrastructures, and a nascent regulatory framework. Therefore, it is imperative to revisit the key aspects of orphan drug development to fulfill the unmet needs of such patients suffering from various rare diseases.

Keywords: Drug development, orphan drugs, patient care, rare diseases

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INTRODUCTION

Rare disease, by definition, is harbored by a small number of patients in a defined geographical area. However, the criteria to define rare diseases may vary from region to regions such as affecting fewer than 200,000 people (6.4 in 10000 people) as specified by the Orphan Drug Act 1983 in the USA or no more than 5 in 10000 people in the EU.[1,2] However, the cumulative estimate of people having such disease tends to be almost 450 million globally (~6% of the global population).[3] This huge number is attributed to the lack of development of the novel orphan drugs attributed to lack of adequate knowledge in the scientific basis of the disease, various hurdles in research and development of drugs, nascent regulatory framework as well as deficient reimbursement procedures. The aforementioned issues pose an impedance for any pharmaceutical company to develop or market any intended drug for such condition. The tendency to avert from such activities by the manufacturers justifies the labeling of such disease and drugs, respectively, as "orphan disease" and "orphan drugs."

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RECENT DEVELOPMENTS IN ORPHAN DRUG RESEARCH: A GLOBAL PERSPECTIVE

The aforementioned challenges necessitate innovative solutions to hasten orphan drug development. It ranges from the inclusion of regulatory solutions to innovative trial design as well as incorporating inputs from different collaborators and stakeholders. Some key activities related to orphan drug development are discussed below.

Regulatory assistance

Regulatory bodies can ease the development as well as approval process providing diverse innovative solutions to tide over the aforementioned issues. Regulatory cooperation by the Food and Drug Administration (FDA) has enthused approval and marketing of over 600 products for orphan disease in the US since 1983. With the prevailing COVID-19 pandemic in 2020, the FDA approved 32 orphan-designated drugs and biological products, to mark sustained progress in orphan drug research and development.[4] A rare disease hub was created by the office of the Center for Drug Evaluation and Research to assess marketing applications for certain rare diseases. It collaborated with a rare disease team, receiving support and assistance for enabling a rare disease policy.[4] To keep up the pace with the increase in the application in subsequent years, the orphan drug modernization pilot program was launched by the FDA to review all applications within a stipulated time of 90 days irrespective of the volume and complexity of the application.[5] Moreover, an online portal was launched in November 2020 to shift to online cloud-based online portal submission from the traditional paper-based application in the context of the pandemics raging through the globe.[6] Regulatory bodies such as the European Medicines Agency (EMA) engage with their international counterparts such as the FDA and the Japanese Ministry of Health, Labour and Welfare for better dissemination of pertinent knowledge and experience, promoting collaboration as a tool in the process of regulatory solutions.[2]

Financial support

Any pharmaceutical company faces hardship in the recovery of the cost of research and development due to a small number of target population harboring the disease of interest representing from sparse geographical location. This can lead to an exorbitant price of the drug imposing a hindrance to reimbursement procedure, hence limited affordability for the needy patients. Funding is critical to the accomplishment of any such trial as well as to ensure the safety of the trial participants. Regulatory bodies such as FDA has created various incentives such as 7 years of market exclusivity for the orphan drug, 25% tax credit to the development cost in case of clinical research within the US, waiver of the Prescription Drug User Fee Act, providing research grant from the office of the orphan product development as well as regulatory assistance.[7] The Orphan Products Clinical Trial Grants Program continued its existence support to 80 ongoing grants with an additional six new clinical trial research grants in 2020.[4] Moreover, the FDA continued their support in Pediatric Device Consortia grantees to ascertain the development of innovative device solutions for pediatric patients. An additional $1 million was granted more than that of the $6 million annual budget, from which $750,000 was allocated to Pediatric Device Consortia grantees.[4,8]

Similarly, agencies such as EMA endorse orphan drug research and development by providing incentives or exemptions from particular fees related to product development or regulatory clearance. For example, applicants from the academic sector are eligible to receive free protocol assistance for developing orphan medicine since June 2020. Similarly, the agency provides further incentives including administrative support to micro-, small-, or medium-sized enterprise. Sponsors can enjoy 10 years of market exclusivity for an orphan-designated product. Furthermore, if any information derived from the pediatric investigation plan is incorporated into the product information of any orphan drug, an additional 2 years of market exclusivity is ascertained.[2]

Patient centric approach in clinical development

Patient centricity in clinical trials is now being greatly emphasized in modern-day drug development. It has been implemented by the utilization of many strategies including the incorporation of electronic patient-reported outcome, engagement with patient advocacy groups. Conducting clinical trials related to orphan diseases are often challenging as a very few numbers of patients are affected by rare disease across sparse geographical areas. In such circumstances, patients or related caregivers become very much influential to the sponsors or regulatory authorities. Often due to the feeling of being isolated, such patients indulge in creating many offline or online platforms for people like them as a platform to share their experiences and stories. Hence, they can be very well informed about their condition which eventually paves the way for their scientific contribution toward stakeholders, i.e., protocol designing, defining meaningful endpoint, and sharing of study results.[4,9] Regulatory authorities such as FDA have recently created an online platform named "FDA Rare Disease Photo and Video Project" to capture real-time patient stories as well as to share the working experience of

FDA staff.[4] For that purpose, the office of patient affairs bolsters patient centricity by arranging different sessions with patients, caregivers, and FDA staff.[10]

Globally, various nonprofit organizations including European Organisation for Rare Diseases and National Organization for Rare Disorders promote patient advocacy including patient assistance, information sharing, or networking in between different patient groups and also support research and regulatory activities in Europe and the USA, respectively.[11,12]

However, patient centricity in orphan drug development is grossly under-represented. As previously mentioned, various Patient Reported Outcome (PRO) measurement (PROM) is pertinent to the clinical development of orphan medicine in the context of paucity in the precise guideline on the development and validation of such outcome. A literature review conducted by Lanar *et al.* showed a lack of PROM utilization in various labeling claims, ClinicalTrials.gov entries, and other relevant literature. For example, PROM was included in the label of 17.4% orphan drugs with labeling claims in FDA or EMA. There was also scarce use of disease-specific, validated PROM scales in the label (9 out of 45, 20%). Table 1 highlights various solutions based upon the assumption of different outcomes that will enable stakeholders to assess treatment benefits.[13]

Table 1: Different outcomes to assess treatment benefit deemed important from the stakeholder point of view and their solution, proposed by Lanar *et al*.[13]

Outcomes	Methods suggested
Disease burden and extent of unmet need	To use generic, well-validated, widely used measure of HRQoL
Treatment impact and specific hypothesis on drug efficacy	To use highly specific, well-validated measure selective to a body function. For example, visual functioning, hand functioning, and cognitive function
Patient perception of change in bodily function or symptoms	To use study-specific diaries or notes to capture variation in symptom frequency and severity along with their impact on patient's daily activities
Documentation of meaningfulness of the changes	Collection of feedback from the patients about their appreciation and judgment of risk-benefit derived from the specific treatment in a trial. For example, qualitative interviewing of the patients in a clinical trial setting

HRQoL: Health-related quality of life

Promotion of International Collaboration and Creation of Task Force

The International Rare Diseases Research Consortium, an amalgamation of international research collaboration, has taken notable initiatives to foster orphan drug development. For such purpose, the Orphan Drug Development Guidebook was launched to assemble available tools or "building blocks" across the USA, the EU, and Japan to establish a framework.[14] For example, in the discovery phase of an orphan drug, five groups of building blocks are summarized into "START" – STakeholders mapping, Available information on the disease, financial Resources, Target patient value profile. The need for gap analysis is prioritized in the absence of important stakeholders' representation like patient groups, lack of relevant disease information such as natural history, selection of biomarker, and clinical outcome of interest. For example, the FDA's Orphan Products Grants Program has recently introduced a request for application to include natural history studies.[4] This will generate historical control groups in the absence of traditional controls in the context of paucity in the comparator intervention, adding scientific as well as ethical value in orphan drug development. Similarly, the FDA is working to develop a standard core set of clinical outcome assessments (COAs) tailored for specific disease indication, which is intended to be publicly available at minimal or no cost.[15] One such initiative, the Rare Disease COA Consortium, has done its first phase of landscape analysis to assess daily function in pediatric age groups by analyzing outcomes such as self-care, fine, and gross motor functions.[4]

In the regulatory process, an earlier regulatory interaction is deemed necessary. Earlier interaction support is currently available in the USA and Europe – FDA INTERACT meeting and EMA Innovation Task Force. For further ease in approval, increased engagement with regulatory bodies was adjudged significant, for example, protocol assistance from the EMA, type C meeting with the FDA, and consultation with the Pharmaceuticals and Medical Devices Agency in Japan.[15] Early access to the orphan drug, even before reimbursement decision, is imperative in the context of high unmet medical need. Currently, the EMA promotes compassionate use of such drugs for patients in need, before any formal regulatory approval is established.[16]

The Indian scenario

Extrapolation from the global estimate of rare diseases depicts about 70 million people affected by rare diseases.[17] Therefore, rare disease management is poised to be a huge burden given such a huge number including many undiagnosed in the context of paucity in resources spent in research and development. However, different initiatives have been promulgated by various organizations that could be noteworthy.

Indian Council of Medical Research initiative

The Indian Council of Medical Research (ICMR) along with AIIMS, JNU, and PRESIDE launched the National

Initiative for Rare Diseases to create the first-ever "Indian Rare Disease Registry" in 2017. The purpose of such a registry is to identify patients with rare diseases to enable pertinent understanding of patient and disease characteristics, which eventually pave the way for utilization of such data for research purposes and policy framing.[18] Although it did not have any pivotal contribution to date, the National Policy for Rare Diseases, 2021, has reiterated that it will enable ICMR to create a hospital-based national registry with the engagement of centers involved in the diagnosis and treatment of rare diseases.[19]

A targeted literature review by Pearson *et al.* endorsed the utilization of long-term patient registry data to facilitate the understanding of natural history and epidemiology data in the context of a rare disease. This can facilitate collection as well as comparison of treatment modalities in real-world patient data with the clinical trial findings using approaches such as matching-adjusted indirect comparisons.[20]

Nongovernment organization initiatives

Like the US and European organizations previously described, the Organization for Rare Diseases India is a national umbrella organization to promote enriched care for people suffering from rare diseases.[21] Activities such as engagement with various national and international collaborators, development and implementation of public policy, encouraging clinical trial, and research activities are prioritized to ensure patient centricity.

Among its notable activities, India's "first-of-its-kind" online questionnaire-based survey was conducted in a well-represented sample, to reflect the baseline knowledge and awareness status related to rare diseases including scope for improvement.[22] Most of the respondents including some of the medical professionals were unacquainted with various basic knowledge and activities related to the rare disease. A majority of the respondents opted for awareness and educational programs to be prioritized in the country followed by the establishment of improved diagnostic facilities.[22]

Contribution of manufacturers and patient groups

Various projects of pharmaceutical companies such as Sanofi Genzymes's India Charitable Access Program, Shire HGT's Charitable Access Program, and Protalix Biotherapeutics have provided improved access to enzyme replacement therapies in various lysosomal storage disorders.[23] However, such charitable programs have a minimal impact given the huge population size of India. Therefore, the contribution of various patient groups is deemed pivotal in rare disease research in India.

An interview-based study, conducted by the Institute of Bioinformatics and Applied Biotechnology, Bangalore, included 19 patient organizations to highlight various aspects of their involvement in rare disease research. Most of the representatives, having been affected directly or indirectly by a rare disease, highlighted a lack of awareness among health-care providers including the high cost of treatment due to lack of health insurance and dearth of research due to the absence of prevalence data. Active involvement of government in the aforementioned activities is therefore anticipated. Institutionalization of various patient group activities, i.e., in policy framing like various other developed countries, should be prioritized.[24]

Role of research on genomics

India, being a huge and diverse country, is hugely burdened by rare diseases attributed to genetic diversity. Therefore, the knowledge of genomics can facilitate scientific understanding as well as research activities for such diseases. The Genomics for Understanding Rare Diseases: India Alliance Network is one such pan-Indian initiative that includes activities such as reporting, community screening, disease modeling, creation of registries, and training of physicians.[25] One of its major successes was the detection of homozygous variation in the MLC1 gene of six children suffering from leukodystrophy at the Nalband community.[25] Genomics and other Omics tools for Enabling Medical Decision is another project adopted by the Council of Scientific and Industrial Research (CSIR) to provide low-cost diagnostic genetic assays in the country. It can help early identification and screening of rare genetic disorders. For example, it revealed the hidden burden of the India-specific rare disease spinocerebellar ataxia 3, known as Machado–Joseph disease in 100–200 families of a close-knit community in Maharashtra.[26] Moreover, the creation of a whole-genome dataset is attempted by programs such as GenomeAsia100k and "Genomics for Public Health (IndiGen)" by CSIR.[25]

Role of government

The research and development activities for rare diseases have been indulged by various rules or policies put forth by the government. The New Drugs and Clinical Trials Rules, 2019, published by the Ministry of Health and Family Welfare, has defined rare disease as a disease that does not affect more than 5 lakh persons in India. Moreover, provision for fast track approval process has been encouraged including a complete waiver for clinical trial filing. Sponsors are allowed to apply to the Central Licensing Authority (CLA) for expedited review, even to get exemption from conducting local clinical studies or phase IV on the satisfaction of CLA.[27]

Finally, the recently published National Policy for Rare Diseases, 2021, has culminated hope for progress in such a field.[19] Some notable proposals, put forth by the policy, are discussed below:

- The cumulative data on people suffering from rare diseases are grossly lacking in India. Inadequate epidemiological data related to the prevalence and incidence of diseases obscure the understanding of the true burden of a disease, i.e., number of patients suffering from such diseases. Therefore, it is imperative to carry out systematic epidemiological studies or to create various registries as previously described, to ascertain the true number of patients harboring any orphan disease of interest in the country
- However, this policy is the very first to create a list of rare diseases in the country utilizing the scientific data by the technical committee, which will also be subjected to further modification and update
- Infrastructure development, as well as capacity building of all stakeholders, is also supported by the setup of various centers of excellence (CoEs) under rare disease policy and Nidan Kendras under the Department of Biotechnology. To date, 8 CoEs are established around the country to promulgate research in low-cost diagnostics and therapeutics including diagnosis and treatment of rare diseases and training and education for the involved stakeholders
- Unlike in the developed countries, optimization of the fund in a resource-compromised setting like India necessitates a more diligent approach. Because of the limited resource, most of the funds are utilized for the promotion of the intervention that would satisfy the health needs of the majority of the population. However, various financial schemes have been proposed by the Government of India to primarily support patients suffering from rare diseases. Under the Umbrella Scheme of Rashtriya Arogya Nidhi, financial support up to Rs. 20 lakh is provided for the diseases that require a one-time treatment. However, such aid is intended for only 40% of the country's population, who are eligible under Ayushman Bharat Pradhan Mantri Jan Arogya Yojana
- Alternate funding mechanisms via the creation of digital platforms will prompt voluntary individual and corporate funding in the context of constrained resources. The primary purpose of such funding will be the treatment cost of the patients with the leftover funds to be used for research purposes
- To propagate research and development activities in rare diseases, ICMR, Department of Biotechnology, Department of Pharmaceuticals, Department of Science and Technology, and Council of Scientific and Industrial Research will be engaged. An integrated approach will be promulgated in collaboration with various research organizations, funding agencies, and pharmaceutical companies. Repurposing of already approved drugs and use of different biosimilars for orphan indication will be adjudged. Local development and manufacturing of drugs at an affordable price will be enthused. There will also be a formal request to the Ministry of Finance to reduce the custom duties to boost up the import.

However, unlike FDA and EMA, there is no formal regulatory guideline on protocol assistance or tax concession or proposal of financial incentives by CDSCO. Therefore, the regulatory framework in India for the overview of the whole process is in a very nascent phase, which needs to get strengthened in the impending future.

As previously discussed, a concerted approach is deemed significant to propel rare disease research in the country. In their article, Taneja *et al.* proposed an effective RECIPE to be included in any policy framework adopted in India, which effectively paves the way for "cure for all" in the country.[28] The approach is mentioned in Table 2.

COMMENTS

The development of an orphan drug is a daunting task with so many challenges to be critically managed. The stakeholders including sponsors, regulatory agencies, and contract organizations have adopted innovative solutions to propagate such development. Developing countries like India can thrive in this disease space acquiring knowledge and experience gradually at par with the Western countries. More scientifically sound, rational, timely development aligned with patient need with proper funding and infrastructure should fulfill the unmet need of the millions suffering from such diseases globally.

Table 2: Details of the "RECIPE" approach to be included in any policy framework as proposed by Taneja *et al.*[28]

RECIPE approach	Activities
R	Advancement in interdisciplinary Research and knowledge
E	Exchange through research and higher educational centers
C	Capacity building for timely diagnosis and treatment, especially in remote areas
I	Innovation and economic Incentive to prompt domestic discovery and development of cost-effective treatments
P	Public awareness and dissemination of information
E	Engagement of patients and patient groups for effective policy formation

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Conflicts of interest
There are no conflicts of interest.

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