Shining light on the global network of rare diseases: Unveiling the 'rare' in not so rare


Anju Jose[1]*, Seema S Rathore[2]

[1]Department of Pharmacy Practice, College of Pharmaceutical Sciences, Dayananda Sagar University, Bengaluru, Karnataka

[2]Department of Pharmaceutics, College of Pharmaceutical Sciences, Dayananda Sagar University, Bengaluru, Karnataka

Email: anjuclaps@gmail.com

Abstract

Orphan drugs developed to treat rare diseases represent a vital, yet often overlooked facet of modern healthcare. Rare diseases, affecting a small percentage of the population, pose significant challenges for individuals and healthcare systems. Despite their rarity, collectively, rare diseases impact millions worldwide. This review explores the interconnected realms of orphan drugs and rare diseases, defining their significance, the challenges faced by patients, and the pivotal role of orphan drugs in addressing unmet medical needs. Through legislative incentives and targeted research efforts, orphan drugs offer hope to individuals with rare diseases, providing tailored treatments and improving quality of life. Understanding and addressing the needs of this patient population are crucial steps toward achieving health equity and advancing healthcare innovation.

Keywords: Rare disease, Orphan drugs, healthcare, preventive measures, regulatory aspects

1. Introduction

Rare disease (RD) and orphan drugs (OD) are interlinked aspects of healthcare that are sometimes overlooked but are vital in enhancing the lives of individuals grappling with rare and frequently incapacitating conditions. An RD has no accepted or common definition. Its definition varies depending on the country and can be expressed as either absolute prevalence or prevalence per 10,000 people. The best definition of an RD is one that considers a nation's resources, population, and healthcare system (1). There are approximately 5,000 to 8,000 rare diseases, with about 7,000 lacking effective treatments. Overall, 300 million individuals worldwide are affected by RDs, with half of them being children, and 30 percent of this population will succumb to their condition before reaching the age of five (2). Over 5,000 medicines and biologicals are used to treat RDs (3) (Figure 1). Any medical product intended for a rare condition or one for which there is currently a lack of effective diagnostic, preventive, and therapy options is known as an OD (3). The European Medicines Agency and the United States Food and Drug Administration (USFDA) have approved a substantial number of ODs, and medications for RDs during the last 20 years (4). The proportion of medications used for oncology, infectious illness, paediatric-onset disease, and neurology has increased significantly and the prevalence of RDs can vary widely depending on the specific condition and geographic region (5) (Figure 1, 2).

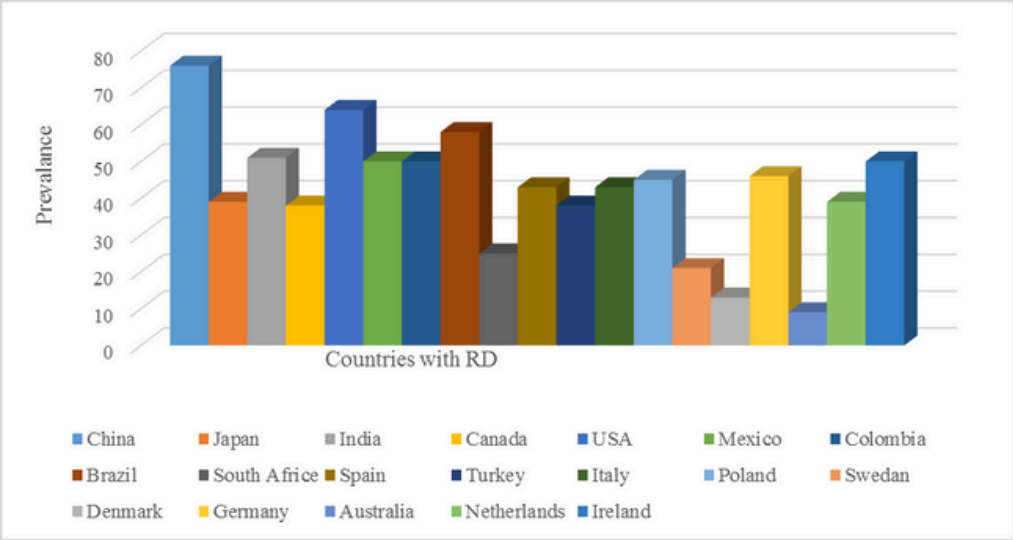

Figure 1. Data on the prevalence of RDs in different countries

Figure 2. RDs with available treatment options

Although very challenging, clinical research for orphan pharmaceuticals is exciting. It doesn't have a single feature that is particularly unique; rather, it encompasses the majority of the obstacles, including design, results, hiring, ethics, cost, probability, and predictability of success. Lack of awareness among primary care providers, inadequate screening, and inadequate diagnostic facilities are only a few of the challenges linked with early detection of RDs. Because of the low patient numbers and infrequently recovered significant expenditure, the rare occurrence of RDs frequently discourages firms from formulating novel medications. Sponsors are reluctant to design and develop these pharmaceuticals under standard marketing circumstances, leaving them "orphaned". Treatment specific to their disease has been administered to less than 10% of patients globally who suffer from RDs (3).

2. Regulatory landscape

The OD Act in the United States of America (USA) was enacted in 1983. The USA's pioneering legislation on OD was later adopted by five regions: Australia, the European Union (EU), Taiwan, and Japan. The same legislation has been developed in Singapore, Canada, and Russia, with plans to

implement their regulatory frameworks in the future. The legislation enabled the advancement of ODs for the management of RDs. The legal frameworks built in the regions have been modified according to their circumstances and needs, creating a wide range of options for the development of ODs. The USA had the highest number of orphan pharmaceuticals however, Japan and Taiwan had higher percentages of approved ODs compared to recognize ones (6).

The OD Act is designed to encourage the development of drugs, diagnostics, and vaccines to enhance treatment choices for rare illnesses by recognizing them as ODs. It is usually regarded as tremendous accomplishment in promoting research and development into RDs. These regulatory requirements can thus be considered highly effective in fostering orphan medication research (7).

The main objective of the USFDA must be to support advancements in treatments for rare illnesses by encouraging reliability, uniformity, and reasonable adaptability in the regulatory procedure within and among its review divisions (8). From the regulatory stage, the approach to developing and marketing orphan pharmaceuticals can be categorized into three separate stages (Figure 3) (9).

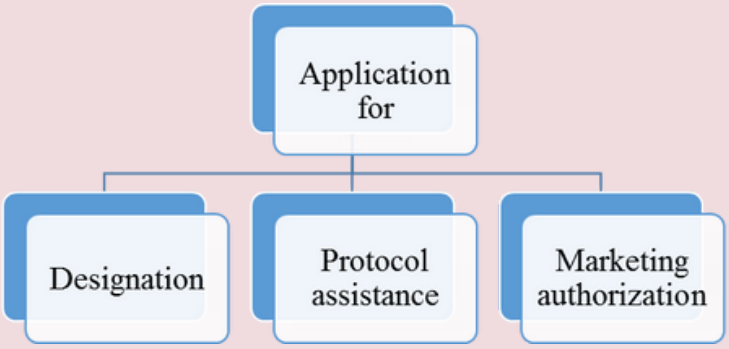

Figure 3. Stages of regulatory approach to developing and marketing OD

The EU legislation implemented the Orphan Regulation in 1999, and it was evaluated by the European Commission (EC) along with the Paediatric Regulation. Both legislations aim to tackle the scarcity of medicines accessible to the group of patients in question, and they frequently treat the same fields of therapy, as many disorders affecting children are rare. The EC has established several regulations, some of which are "Regulation (EC) No 847/2000, Regulation (EC) No 726/2004, Regulation (EC) No 2049/2005, and Regulation (EC) No 1901/2006" (10).

3. Prevention

Preventive measures for RDs can vary widely depending on the specific disease in question, its causes, risk factors, and available medical knowledge. Preventing and managing neonatal and childhood disorders are crucial aspects of RD management. (Table 1) (1).

Table 1. Preventive measures for the occurrence of RD in special population

Precautions	Implementation
Primary Prevention	Preventing the onset of the disease Eg: Avoiding pregnancy at an older age
Secondary Prevention	Avoiding the birth of affected foetus 1. Prenatal screening 2. Prenatal diagnosis by invasive testing (Chorionic Villus sampling & Aminocentesis) 3. New born screening 4. Early postnatal diagnosis & treatment

4. Drug development process (orphan drugs)

Drug development is a multifaceted, resource-intensive, and time-consuming procedure across all disease conditions. However, developing medications for RDs poses additional hurdles because of the limited number of patients, inadequate understanding of the disease, diverse clinical manifestations, and varying disease progression. Most health authorities encourage the development of orphan medications by providing a variety of incentives to firms producing treatments or diagnostics for uncommon diseases. The incentives are given as tax credits, grant funding and fee waivers (11,12). The regulatory bodies also include rapid approval, fast-track assignment, and innovative treatment categories.

The drug development process for OD can be simplified by using a checklist with the abbreviation **START** (11).

- **ST- ST**akeholder mapping
- **A**vailable information on the diseases
- Financial **R**esources
- **T**arget patient value profile

Producing strong preclinical data is a critical component of successful drug discovery. It is always ideal to employ new strategies that make the process quicker, save time and money on research, and get to market as soon as possible. The newer approaches used for preclinical studies are Induced pluripotent stem cells, Organoids and organs-on-a-chip, Modeling and simulation, and 3D cell cultures (13).

Following a satisfactory preclinical evaluation, clinical trials are carried out to determine the safety and efficacy profiles of the medication. In a typical procedure, sponsors need to submit an Investigational New Drug application, which contains the findings of the preclinical studies. In rare disease (RD) clinical trials, the low disease prevalence results in a small number of people affected by each ailment, which is exacerbated in the paediatric population of RDs (13). The small sample size allows for tailored clinical trials for orphan diseases (ODs) and RDs. This can be accomplished by multicentre trials, accessibility and incorporation of additional geographical areas, statistical trial designs (Bayesian approach), adaptive seamless designs, usage of biomarkers, and genetic and biotechnological tools (14).

5. Indian scenario

There is a dearth of information about the prevalence of several diseases that are uncommon worldwide in India. In tertiary hospitals, the cases that have been found thus far have been diagnosed. The lack of epidemiological data on the incidence and prevalence of rare diseases hinders understanding the extent of the burden these conditions impose and the formulation of a clear definition.Only a small number of illnesses that are regarded as rare worldwide have been identified in India's tertiary care facilities thus far, while the range may include 7000–8000 disorders. Under the Unique Methods of Management and Treatment of Inherited Disorders scheme, the Department of Biotechnology established Nidan Kendras (NKs) to provide genetic testing and counselling services. These NKs offer genetic testing, RD screening, and counseling (1).

6. Rare diseases team

The world envisioned by the Sustainable Development Goals includes individuals with RDs and no one is left behind. An illness does not become irrelevant or less significant than diseases that afflict millions of people just because it affects a smaller number of people (15). With this aim, a RDs Team was formed with the mission – “to help patients suffering from uncommon conditions by expediting, supporting, and facilitating the development of pharmaceutical and biologic products”

7. Rare disease day

The World RD Day, observed on the last day of February each year, is an opportunity to raise awareness of RDs that affect over 300 million people globally. The theme for 2024 was "Share your Colours," which aimed to raise awareness of the difficulties associated with having a RD. It is typical for some RD patients to have symptoms for an extended period before receiving a correct diagnosis, as there are almost 7,000 identified RDs, the majority of which do not have approved therapies. The goal of RD Day is to bring attention to and encourage support for individuals facing uncommon medical conditions worldwide. This year, February 29th, the rarest day of the year, is the final day of February, when it took place (16).

8. Success stories

Orphan medications have emerged as a key element in the management of RDs, offering hope and assistance to patients who previously had few options. Over 5000 medicines and biologicals are used to treat RDs. The proportion of medications used for oncology, infectious illness, paediatric onset disease, and neurology has increased significantly. The substantial rise in overall ODs within the last four decades indicates that there will be an upward trend in categories, resulting in increased authorization for drugs and biologics specifically developed for diagnosing, preventing, and treating RDs in the upcoming decades (17,18).

9. Challenge and future perspective

The challenges associated with OD and RD include uncertainty in the pathophysiology of the disease, lack of approved preclinical models, unavailability of benchmark reference drugs, unexpected natural origins of the disease, absence of criteria for diagnosis, endpoint selection, patient availability, and recruitment, identifying suitable sites, inadequate data, and commercialization (19,20).

The International RD Research Consortium has various goals for the future perspective (21). The goals include:

- Discovery of mechanism of RD
- Diagnosis accessibility
- Global network of undiagnosed diseases
- Educating physicians and engaging the patients
- Drug development process
- Promising advances in the development of therapies
- Engaging patients and regulatory bodies
- Evaluating the consequences of prognosis, treatment of disease
- Using tools like NIH Genetic Testing Registry and RARE Best practices

10. Conclusion

OD are medications developed for RDs that affect a small number of individuals. These drugs are granted special status by regulatory agencies to incentivize their development, such as extended market exclusivity, tax incentives, and reduced regulatory fees. The successful development and approval of OD have had a significant impact on patients with RDs by providing them with access to treatments that were previously unavailable. These drugs have improved the quality of life, increased life expectancy, and addressed unmet medical needs for individuals with RDs. Additionally, OD have led to advancements in personalized medicine and have paved the way for innovative therapies in the field of RDs.

References

1. National Policy for Rare Disease 2021 [Internet]. India [cited 2024 May 11]. Available from: https://rarediseases.mohfw.gov.in/uploads/Content/1624967837_Final-NPRD-2021.pdf,
2. Chan AY, Chan VK, Olsson S, Fan M, Jit M, Gong M, Zhang S, Ge M, Pathadka S, Chung CC, Chung BH. Access and unmet needs of orphan drugs in 194 countries and 6 areas: a global policy review with content analysis. Value in Health. 2020 Dec 1;23(12):1580-91.
3. Chung CC, Hong Kong Genome Project, Chu AT, Chung BH. Rare disease emerging as a global public health priority. Frontiers in public health. 2022 Oct 18;10:1028545.
4. Costa E, Moja L, Wirtz VJ, van den Ham HA, Huttner B, Magrini N, Leufkens HG. Uptake of orphan drugs in the WHO essential medicines lists. Bulletin of the World Health Organization. 2024 Jan 1;102(1):22.
5. Fermaglich LJ, Miller KL. A comprehensive study of the rare diseases and conditions targeted by orphan drug designations and approvals over the forty years of the Orphan Drug Act. Orphanet Journal of Rare Diseases. 2023 Jun 23;18(1):163.
6. Huang YJ, Chao WY, Wang CC, Chang LC. Orphan drug development: The impact of regulatory and reimbursement frameworks. Drug Discovery Today. 2022 Jun 1;27(6):1724-32.
7. Pryde DC, Groft SC. Definitions, History and Regulatory Framework for Rare Diseases and Orphan Drugs.
8. Boat TF, Field MJ, editors. Rare diseases and orphan products: Accelerating research and development. URL: https://www.ncbi.nlm.nih.gov/books/NBK56185/
9. Shah RR. Regulatory framework for the treatment of orphan diseases. Fabry disease: perspectives from 5 years of FOS. 2006. URL: https://www.ncbi.nlm.nih.gov/books/NBK11567/
10. Legal Framework: Orphan Designation [Internet]. The Netherlands: European Medicines Agency; [cited 2024 May 11]. Available from: https://www.ema.europa.eu/en/human-regulatory-overview/orphan-designation-overview/legal-framework-orphan-designation#review-of-orphan-regulation-11969
11. Orphan Drug Designation for Rare Diseases [Internet]. Cytel; 2024 April 10 [cited 2024 May 11]. Available from: https://www.cytel.com/blog/orphan-drug-designation-for-rare-diseases
12. Jonker AH, Batista L, Gabaldo M, Hivert V, Ardigo D, IRDiRC ODDG TF and IRDiRC TSC. How to START? Four pillars to optimally begin your orphan drug development. Orphanet Journal of Rare Diseases. 2023 Aug 3;18(1):229.
13. Rare Diseases: Pre-Clinical Studies And Clinical Trials In Orphan Drug Development [Internet]. Credevo; [cited 2024 May 12]. Available from: https://credevo.com/articles/2019/05/15/rare-diseases-pre-clinical-studies-and-clinical-trials-in-orphan-drug-development/
14. Bruco A L P. Orphan Drugs: Development Process and Clinical Use. Universidade of Coimbra, June 2018: [cited 2024 May 12]. Available from: https://estudogeral.uc.pt/bitstream/10316/84645/1/Inforestudante_Orphan%20 Drug Development
15. Rare Diseases Team [Internet]. U.S. Food and Drug Administration; 2023 Aug 29 [cited 2024 May 13]. Available from: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/rare-diseases-team
16. Rare Disease Day 2024 [Internet]. Biomed Central; [cited 2024 May 13]. Available from: https://www.biomedcentral.com/p/rdd-2024
17. Miller KL, Fermaglich LJ, Maynard J. Using four decades of FDA orphan drug designations to describe trends in rare disease drug development: substantial growth seen in development of drugs for rare oncologic, neurologic, and pediatric-onset diseases. Orphanet journal of rare diseases. 2021 Jun 9;16(1):265.
18. The Rise of Orphan Drugs: Opportunities and Challenges in Rare Disease Treatment [Internet]. Rubio; [cited 2024 May 13]. Available from: https://www.laboratoriosrubio.com/en/rare-diseases/
19. Budarapu D. Challenges in the Research and Development of Orphan Drugs: A Review. Journal of Pharmaceutical Research International. 2022 Nov 17;34(53B):1-6.
20. Berthelot S, et al. Rising to the Challenges of Developing Rare Disease Treatments [Internet]. Parexel International, Inc; [cited 2024 May 13]. Available from: https://globalforum.diaglobal.org/issue/february-2020/rising-to-the-challenges-of-developing-rare-disease-treatments/
21. Austin CP, Cutillo CM, Lau LP, Jonker AH, Rath A, Julkowska D, Thomson D, Terry SF, de Montleau B, Ardigò D, Hivert V. Future of rare diseases research 2017–2027: an IRDiRC perspective. Clinical and translational science. 2018 Jan;11(1):21.