The Journal of Multidisciplinary Research (TJMDR)

Content Available www.saap.org.in ISSN: 2583-0317

PHARMACEUTICAL STRATEGIES IN ORPHAN DRUG DEVELOPMENT

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Article History: Received: 24 Jan 2026 Revised: 11 Feb 2026 Accepted: 16 Mar 2026

Abstract: Pharmaceutical medicines known as orphan medications are created to treat uncommon illnesses that only a small percentage of people have and frequently have no proven treatments. Only a small number of licensed treatments are accessible despite the rising prevalence of rare diseases worldwide, mostly because of financial, regulatory, and scientific obstacles. With an emphasis on developing therapeutic modalities, technological breakthroughs, and regulatory frameworks, this paper offers a thorough analysis of orphan drug development. Treatment options for formerly untreatable uncommon diseases have increased due to recent trends showing a diversity of pharmacological modalities, including small molecules, gene and cell therapies, nucleic acid-based medicines, monoclonal antibodies, and synthetic proteins. Orphan drug approvals in the US have been greatly sped by regulatory incentives like the Orphan Drug Act, and development has been further aided by changing trial designs like n-of-one and expedited review procedures

Keywords: *Orphan drug, regulatory pathways, treatment, drug development, rare diseases, patient advocacy rare diseases, regulatory.*

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Produced and Published by
South Asian Academic Publications

INTRODUCTION

According to the 1984 revisions to the U.S. Orphan Drug Act (ODA), a medication is deemed an orphan drug if it is not anticipated to be effective within seven years of FDA clearance or if it is meant to treat a condition that affects fewer than 200,000 people in the nation [1]. European Medicines Agency (EMA), European Union (EU) When a medication is created for the diagnosis, prevention, or treatment of a serious or fatal illness that affects little more than 5 out of 10,000 EU members, it is referred to as a "orphan " [2]. Diseases with low population prevalence are considered rare. They are also referred to as orphan diseases, and the medications created to treat them are called orphan pharmaceuticals.

Even though they are considered "rare," 70–96 million people in India, 29 million in Europe, and 30 million in the US have been reported to have uncommon diseases [3].

BACKGROUND

Rare diseases, commonly referred to as orphan diseases, impact a small portion of the population. There are approximately 6,172 distinctive rare illnesses, 71.9% of which are inherited and 69.9% of which have only paediatric onset. Despite their individual rarity, collectively, these diseases affect a significant number of people. According to Orpha net, a database for rare diseases, epidemiological data is available for 63% of the 9,408 clinical entities contained in their database. The development of orphan drugs might be expensive because the unique challenges they present, such as small patient populations and a lack of existing research or data. The Tufts Centre for the Study of Drug Development reports that the time it takes to launch a drug from the initial patent application to the product is 15.1 years for orphan drugs, which is 18% longer than the average time needed for all new drugs. An "orphan drug" refers to a medication developed specifically to treat a rare disease, often considered commercially unattractive due to the small patient population, and the "orphan drug dynamics" refers to the unique challenges and incentives involved in developing such drugs, primarily driven by legislation like the Orphan Drug Act (ODA) [4].

The Orphan Pharma Act of 1983 is regarded as a significant piece of legislation because it addressed issues concerning rare diseases and ailments that had previously gone unnoticed in the pharmaceutical industry.

ADVANCED CELL AND GENE THERAPIES FOR ORPHAN DRUG DISEASES

In the last *5 years, there has been a significant rise in US-FDA approvals of cell and gene therapies for rare disease indications. We have summarized four such approvals, which have utilized the regulatory strategies provided in the guidances. The four case studies represent the most recent approvals at the time of the writing of this manuscript. Moreover, these studies exemplify how rare-disease-specific provisions of the regulatory guidances were effectively utilized for approval.

1. Gene therapy for retinal dystrophy

The regulatory strategy involved obtaining approvals for Priority Review and Break through Therapy designations, since this modality of treatment provided exponential advancement in potential curative treatment of this disease. The pri mary evidence of Luxturna's efficacy was based on a Phase 3 study involving 31 subjects. The trial involved measuring the change from baseline to 1 year in the ability of a subject to navigate an obstacle course at various light levels [5]. In the crossover part of the study with the control group, 93% of the par ticipants showed a gain of vision function for 1 year of follow-up

2. Evrysdi for spinal muscular atrophy (SMA)

In 2020, the US-FDA approved Evrysdi (risdiplam) by Genentech Inc to treat patients 2 months of age and older with SMA. The regulatory pathway was expedited by Orphan Drug and Fast Track and Priority Review designations, since early clinical trial data demonstrated substantial improvement in muscle functions in some patients [5].

3. Therapies for Haemophilia

They are two recent breakthroughs in approving therapeutics treating haemophilia, as these therapies had curative potential for this genetic disease. On 22 November 2022, Hemogenic (ethanologenic Deza proves) by CSL Behring LLC received US-FDA approval for the treatment of adults with haemophilia B. The regulatory strategy involved Priority Review, Orphan Drug, and Breakthrough Therapy designations [6]. Hemogenic utilizes an adeno-associated viral vector to deliver a gene that encodes a blood clotting protein known as Factor

4. Gene therapy for Duchenne muscular dystrophy

In 2021, the US-FDA approved Amonds 45 (casi mersen) injection developed by Sarepta Therapeutics, Inc. for the treatment of Duchenne muscular dystrophy (DMD). This approval was granted through the Fast Track and Priority Review regulatory pathway, as efficacy endpoints were observed early in clinical trials

5. SMN 2 mRNA splicing modifier and SMN1 gene delivery

Risdiplam was approved by the U.S. FDA in 2020 for the treatment of spinal muscular atrophy (SMA). The drug is a small molecule that modifies the splicing of the SMN2 gene, promoting the inclusion of exon 7. Through this mechanism, risdiplam increases the production of full-length, functional SMN protein, helping to compensate for the loss of the SMN1 gene. Prior to the approval of risdiplam, the primary disease-modifying therapy for SMA was nusinersen, an antisense oligonucleotide that also enhances exon 7 inclusion in SMN2 transcripts.

REGULAT ORY DEFINITION AND SPECIAL STATUS OF ORPHAN DRUGS

Regulatory Definition

Definition & Thresholds: Generally defined by low prevalence. In the US, it is a disease affecting < 200,000 people, or more if the drug developer cannot recover costs. In the EU, it is < 5 per 10,000.

Purpose: Incentivizes research and development for diseases otherwise ignored due to low profitability.

Benefits & Incentives:

Marketing Exclusivity: 7 years in the US, 10 years in the EU.

Financial Incentives: Tax credits for clinical trials, waiver of FDA user fees.

Regulatory Assistance: Faster, streamlined, or expedited review processes.

Designation Process: It is a separate process from approval; sponsors must apply to demonstrate the drug's potential for treating a rare condition.

Indian Regulatory Provisions for Orphan Drugs:

The National Policy for Rare Disease 2021 and amendments adopted by India's Central Drugs Standard Control Organization (CDSCO) in 2019-mark important improvements in the regulation and treatment of orphan diseases in India. For the 1st time, India has a precise definition of orphan drugs according to the CDSCO's New drugs and Clinical Trials Rules in 2019. Orphan drugs are defined now as drugs used to treat diseases that affect fewer than 500,000 persons in India [7]. This criterion is consistent with worldwide standards and aids in the identification of drugs designed to treat rare disorders. Indian authorities now have the power to exclude orphan drugs from phase III and IV clinical studies, according to the revised guidelines for clinical trials. In acknowledgment of a significant unmet medical need, manufacturers or sponsors of orphan drugs may petition to India's CDSCO for an expedited review procedure, therefore eliminating the necessity for local clinical trials.

BRIEF OVERVIEW OF PATHWAY FOR DRUG DEVELOPMENT

The primary objective of drug development is to develop a safe and effective treatment for a disease. The process is similar whether the disease is rare or common. Drug development begins with understanding

the disease biology and pathogenesis. Studying disease biology helps identify potential targets for therapy. The first step is designing a drug to prevent disease progression or cure the disease. A suitable drug modality or platform is then selected. Drug modalities include small chemical molecules and synthetic peptides. They also include recombinant biologics and monoclonal antibodies. Other modern approaches include RNA, DNA, small interfering RNA (siRNA), and antisense oligonucleotides.

REGULATORY PATHWAY FOR ORPHAN DRUGS USFDA AND INDIA

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ORPHANDRUG: THE INDIAN SCENARIO AND ITS CHALLENGES

US FDA the US FDA has provided a detailed pathway for orphan drug development. Further, it regularly updates and publishes numerous guidance in this regard. We have not listed this guidance here; rather, we have provided references and a link to these guidance and processes. The reader is also encouraged developing drugs for rare diseases is more complex and expensive than that for common diseases because the underlying mechanisms of many rare diseases are not well understood [8].

ECONAMIC BURDEN AND COST OF TREATMENT FOR RARE DISEASE

According to data from the IQVIA Institute for Human Data Science, global expenditure on orphan drugs exceeded $200 billion in 2020, and it is projected to continue to increase in the coming years. This is partly because of the high cost of individual orphan drugs, which can sometimes reach hundreds of thousands of dollars per patient per year. According to some estimates, FDA-approved treatments are available for less than 5% of rare genetic disorders, although this number may vary depending on the specific populations and data sources. Their product port folios and ensure long terms unstability [9].

COST AND TREATMENT:

Except for Food for Special Medical Purposes (FSMP) for small molecule inborn errors of metabolism, India currently lacks local pharmaceutical manufacturers for uncommon disorders. The annual cost of treating some uncommon disorders for a child weighing 10 kg can range from 10 lakhs to more than 1 crore, with the cost and dosage of the drugs increasing with age and weight. Countries have used a variety of strategies tailored to their specific circumstances to address the issue of high costs [10].

In the United States and Canada, laws such as the Orphan Drug Act (ODA) provide incentives to drug manufacturers to encourage them to develop drugs for rare diseases. In 2019 New Drugs and Clinical Trial Regulations (the "New Drugs and CT Rules") say that an orphan drug is a treatment "designed to treat an illness that affects less than five lakhs (500,000) people in India."

- Patient advocacy and empowerment. Patient assistance programs can provide financial aid, discounts, and subsidies to enable affordable diagnosis, therapy, and treatment. Awareness programs to increase public awareness of rare diseases to reduce stigma and improve access to healthcare services can be transformative to patient and patient family well-being in society [10].
- Patient registries. Patient registries for rare diseases play a pivotal role in research and development. Databases systematically collect and store detailed information from multiple sources, including healthcare providers, hospitals, and individual patients.

These recommendations for access and affordability are just a ‘tip of the iceberg.’ It is critical for stake holders of the government, healthcare, pharmaceutical industry, advocacy groups, international organizations, and philanthropists to create and implement policies that focus on access and affordability. All the major factors individually have made formidable inroads into development of drugs for rare diseases in the past 5 years. It is time to make transformative changes through focused efforts and collaboration.

NATIONAL POLICY FOR RARE DISEASE IN INDIA [2021]

The Ministry of Health and Family Welfare, Government of India, formulated a National Policy for the Treatment of Rare Diseases in 2021. The policy prioritizes research and development of orphan pharmaceuticals along with it also encourage innovation and investment in the discovery of therapies for rare illnesses, including financial incentives for pharmaceutical firms to do research in this field. A hospital-based National Registry for Rare Diseases will be established under the Indian Council of Medical Research (ICMR) to compile the data and create a database of rare diseases, thereby addressing the lack of epidemiological data [11].

The draught National Policy for Rare Diseases was finalized and made available to the public on January 13, 2020, based on the Expert Committee's report and with the approval of the relevant authority, inviting comments/views from all stakeholders, the public, organizations, and States/UTs. For review and

recommendation, the DGHS (Directorate General of Health Services) received comments and suggestions from the general

To combat this, the Indian Council of Medical Research (ICMR) has established a hospital-based National Registry for Rare Diseases, which includes organizations from across the country involved in the diagnosis and treatment of Rare Diseases. This will provide critical epidemiology information for rare diseases.

DISCUSSION

Challenges in treatment

Medication availability and access are critical for reducing morbidity and mortality associated with rare diseases. Despite recent advances, the majority of rare diseases continue to lack access to safe and effective treatments. There are treatments available for less than 5% of the 7000-8000 rare diseases. This study reveals that the modalities used for orphan drug development have been diversified for thepast12years. Small-molecule drugs were still predominant, accounting for two-thirds of the approved orphan drugs in the period of 2011–2014. More recently, novel modal-ities, such as cyclic peptides and proteolysis-targeting chimeras, are emerging. Increased availability of various modalities may further increase the chances of orphan drug development; therefore, orphan drug developers should invest in the development and acquisition of new modality technologies [11].

STRATEGIES AND FUTURE DIRECTION FOR ORPHAN DRUG

Enzyme replacement therapy (ERT) is used to treat lysosomal storage diseases (LSD) caused by lysosomal hydro lased efficiency ERT involves the introduction of a functional enzyme into the body to compensate for deficient or missing enzymes [13, 15]. ERT was first approved in the 1990s for Gaucher disease, and the first ERT drug replaced placenta derived gluceras, with imiglycerase in Chinese hamster ovary cells expressing recombinant human-β-glucocerebrosidase. Pegvaliase is an FDA-approved ERT used in adults with phenylketonuria (PKU) and uncontrolled blood phenylalanine concentrations.

Future directions in orphan drug research can encompass a wide range of innovative approaches. As approximately 80% of rare diseases are estimated to have a genetic origin which can be overcome by adapting gene therapy techniques, including gene replacement, genes licensing and gene editing (e.g., CRISPR/Cas9) [12]. In India, the development of orphan drugs is particularly challenging due to factors such as a large population, resource constraints, and the lack of a clear regulatory path for orphan drug development [16,17]. The annual treatment cost for a young child weighing 10kg for some rare diseases in India might range from18lakhsto 1 crore 70 lakhs. The future of orphan drugs is likely to see a significant focus on personalized medicine, advanced gene therapies, increased collaboration between research institutions and patient advocacy groups [13, 17]. Leveraging big data analytics to identify rare disease populations, and a continued push for global regulatory harmonization to improve access to treatments for patients worldwide, ultimately offering more targeted and effective treatments for rare diseases with improved accessibility [18].

CONCLUSION

Orphan drug development remains a complex and resource-intensive process due to small patient populations, high research costs, limited epidemiological data, and affordability challenges. However, significant progress has been achieved globally through regulatory incentives such as tax benefits, market exclusivity, and expedited approvals. The success of innovative therapies-including gene therapies, biologics, nucleic acid drugs, and targeted small molecules-demonstrates the transformative potential of advanced modalities in treating rare diseases.

In India, initiatives such as the National Policy for Rare Diseases (2021) and regulatory reforms by CDSCO mark important steps toward improving diagnosis, treatment access, and research promotion. Nevertheless, greater efforts are needed to enhance awareness, strengthen legislation, expand financial support, and ensure equitable accessibility and affordability. Compared to the well-established US Orphan Drug Act framework, India is still evolving its regulatory ecosystem.

Modality diversification and increasing global collaboration are expected to expand treatment options while addressing pricing and reimbursement challenges. Sustained policy support, commercialization strategies, and public–private partnerships will be essential to balance the interests of patients, payers, and drug developers. Ultimately, strong regulatory harmonization and innovation-driven approaches are crucial to improving outcomes for individuals affected by rare diseases worldwide.

AUTHOR CONTRIBUTIONS

All authors are contributed equally.

FINANCIAL SUPPORT

None

DECLARATION COMPETING INTEREST

The authors have no conflicts of interest to declare.

ACKNOWLEDGEMENTS

NONE

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