REVIEW ARTICLE

Orphan Drug Dynamics in India: Challenges, Strategies, and Success Story

Megha Patel[1], Hemraj Singh Rajput[1], Yakshi Patel[2]

[1]Department of Pharmacy, Sumandeep Vidyapeeth Deemed to be University, Vadodara, Gujarat, India,
[2]Department of Pharmacy Practice, Parul Institute of Pharmacy, Parul University, Vadodara, Gujarat, India

Abstract

An orphan drug is the pharmaceutical product formulated to treat rare health conditions. This article provides a comprehensive overview of orphan drugs, focusing on their definition, regulatory status, as well as the challenges and initiatives related to orphan drug development and accessibility in India. It highlights the significant improvements in India's regulatory framework for orphan drugs, including expedited review processes and exemptions from certain clinical trial requirements. The article also presents a list of orphan drugs sponsored by Indian companies, demonstrating India's contributions to orphan drug development. Furthermore, it showcases a success story of an orphan drug introduced by Sun Pharmaceutical Industries Limited, emphasizing the importance of research and innovation in addressing unmet medical needs. Finally, future directions in orphan drug research, such as gene therapy and repurposing existing drugs, are discussed, along with the potential of global collaboration and regulatory harmonization to expedite access to innovative therapies for patients worldwide.

Key words: Indian scenario, national policy, orphan drug, rare diseases, regulatory pathways

INTRODUCTION

Definition

U.S FDA

A drug is considered an orphan drug under the 1984 amendments to the U.S. Orphan Drug Act (ODA) if it is intended to treat a condition that affects fewer than 200,000 individuals in the country or if it is not expected to be beneficial within 7 years after FDA approval.[1]

European Union (EU), the European Medicines Agency (EMA)

The drug is known as "orphan" when it has been developed for the diagnosis, prevention, or treatment of a life-threatening or persistently and severely disabling illness that affects no more than 5 in 10,000 EU citizens.[2]

BACKGROUND

Rare diseases, commonly referred to as orphan diseases, impact a small portion of the population.[3] There are approximately 6,172 distinctive rare illnesses, 71.9% of which are inherited and 69.9% of which have only paediatric onset.[4] 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 entitiescontained in their database.[5] The development of orphan drugs might be expensive becausethe 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.[6]

SPECIAL REGULATORY STATUS

U.S. Food and Drug Administration and the EMA provide special regulatory pathways and incentives for orphan drug development.At the sponsor's request, the ODA grants a

Address for correspondence:
Dr. Megha Patel, Department of Pharmacy,
Sumandeep Vidyapeeth Deemed to be University,
Vadodara, Gujarat, India.
E-mail: patelmegha5456@gmail.com

Received: 03-06-2024
Revised: 14-08-2024
Accepted: 27-08-2024

unique status known as orphan designation to a medication or biological product intended to treat a rare condition or illness.[7] Orphan drug designation grants market exclusivity to the drug sponsor for a certain time frame (usually 7 years in the U.S and 10 years in the EU). The ODA provides tax credits for qualified clinical trials, which can help offset the costs of developing an orphan drug[8] It provide exemptions from certain FDA application fees, which can further reduce the financial burden of orphan drug development[9] Funding is available for clinical research on the safety and effectiveness of drugs intended for use in rare illnesses or disorders under the FDA's Orphan Drugs Grants Program.[9]

INDIA'S 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.[10] Orphan drugs are defined now as drugs used to treat diseases that affect fewer than 500,000 persons in India. 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.[11]

ORPHAN DRUG: THE INDIAN SCENARIO AND ITS CHALLENGES

Globally, there are between 7,000 and 8,000 rare diseases identified. There are only a few rare diseases reported in India, mostly those diagnosed at tertiary care hospitals.[12] As a result, there is little information available on the prevalence of rare diseases in India, which makes it difficult to estimate the cost of healthcare and develop effective interventions. Furthermore, without knowing adequate information on disease prevalence, morbidity, and mortality, it is challenging to assess the economic impact of rare diseases on health-care systems and society as a whole. Some of the rare diseases commonly reported in India include primary immunodeficiency disorders, lysosomal storage disorderssuch as Gaucher's disease, Pompe disease, cystic fibrosis, osteogenesis imperfecta, certain forms of muscular dystrophies, and spinal muscular atrophy while other are still unexplored due to lack of awareness among health-care professionals, patients, and policy-makers about rare diseases and orphan drugs.[12]

Due to the small patient populations affected by orphan diseases, clinical trials may be smaller in scale and may utilize alternative study designs to demonstrate effectiveness which is another challenge faced during clinical trial. While India has provisions for orphan drugs within its regulatory framework, such as expedited review and approval processes, there may still be bureaucratic hurdles and delays in obtaining orphan drug designation and approvals. Orphan drugs are sold at high price due to the high costs associated with their development and manufacturing, even after India has provisions for orphan drugs within its regulatory framework, such as expedited review and approval processes. Hence, high expense of orphan drug makes them inaccessible to many patients, especially in a country like India where health-care expenses are a concern. Furthermore, without knowing adequate information on disease prevalence, morbidity, and mortality, it is challenging to assess the economic impact of rare diseases on health-care systems and society as a whole.[12]

IMPLEMENTED STRATEGY FOR ADDRESSING ORPHAN DISEASE IN INDIA

National policy for rare diseases 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. The policy aims to improve access to treatment for patients with rare diseases, offering financial aid and support services.[13] 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.[14]

Awareness programs

There has been an increase in awareness programs for rare diseases in India.[15] Awareness campaigns will be conducted to educate health-care professionals and the general public about rare diseases, promoting pre-marital genetic counseling, early detection, and prevention measures.

Financial assistance

Under the Rashtriya Arogya Nidhi scheme, financial aid of up to Rs. 20.00 lakh will be provided under for the treatment of rare diseases amenable to 1-time treatment.[16]

Research initiatives

The Indian National Science Academy conducted a workshop entitled "To Develop a Scientific Program for Research on Rare Diseases" in 2016.[17] The workshop discussed rare disease definition, awareness, research avenues, policy framework, and legislation for State involvement in fulfilling rare diseases' special needs. Education and awareness initiatives will be encouraged, including the establishment of Department of Medical Genetics in medical colleges to bolster manpower and knowledge.

Affordable drugs

The government will also work to encourage domestic research and production of affordable rare disease drugs, and it will ask the Ministry of Finance to lower the duties on imported rare disease drugs. The Department of Pharmaceuticals is implementing the Production Linked Incentive Scheme for Pharmaceuticals with a total financial investment of Rs. 15,000 crore and for the period of FY 2020–2021 to FY 2028–29 in an effort to expand the nation's pharmaceutical industry to Atmanirbhar.[18] Three distinct kinds of drugs are covered under the program. Orphan medications, particularly those used to treat rare disorders, are one of the product groups under Category-1. For a period of 6 years, the plan offers incentives depending on their increased sales.[18]

Infrastructure development

Premier government hospitals will select a few chosen Centers of Excellence, receiving financial support for infrastructure development and management of rare diseases. A digital platform will be established to connect these Centres of Excellence with potential donors for funding rare disease treatments, ensuring transparency by linking funding to the ICMR registry.

Collaboration with international entities

India is also collaborating with international entities to learn from their experiences and implement best practices in the field of rare diseases. These strategies represent a comprehensive approach to addressing the challenges posed by orphan diseases in India. However, there is still a lot of work to be done to improve the diagnosis, treatment, and care of patients with these rare conditions.

STATISCS

As of 2023, there were 1200 marketed orphan drug, of which U.S. dominated development of orphan drugs.[19] Table 1 shows the list of orphan drug sponsored by India, of which one got marking approval.

SUCCESS STORY OF ORPHAN DRUG

Sun Pharmaceutical Industries Limited introduced a groundbreaking product called SEZABYTM (phenobarbital sodium) in the United States in January 2023.[20] This product is specifically designed to treat neonatal seizures, making it the first and only FDA-approved medication for this purpose.[20] SEZABY is formulated to effectively address seizures in both term and preterm infants, providing a much-needed solution for this vulnerable patient population. One of the key features of SEZABY is its unique formulation. It is a benzyl alcohol-free and propylene glycol-free powder for injection, containing phenobarbital sodium. This formulation been accorded orphan drug designation by the US FDA, recognizing its importance in treating neonatal seizures.[21] The absence of benzyl alcohol and propylene glycol in SEZABY ensures that it is safe and well-tolerated by neonates. The approval of SEZABY was based on the results of a phase 2 study called NEOLEV2, which compared phenobarbital tolevetiracetam as a first-line therapy for newborn seizures.[21] The study demonstrated that 73% of neonates treated with phenobarbital became seizure-free within 24 h, compared to only 25% in the levetiracetam group.[22] This clinical evidence highlights the efficacy of SEZABY in managing neonatal seizures and reinforces its importance as a treatment option. It is important to note the safety information associated with SEZABY.

Common adverse reactions include abnormal respiration, sedation, feeding disorder, and hypotension.[23] In addition, SEZABY has specific safety warnings regarding its concomitant use with opioids, as well as the potential for dependence, withdrawal reactions, and misuse. Health-care professionals should be aware of these safety considerations when prescribing SEZABY to neonatal patients. The significance of SEZABY's approval cannot be overstated. Sun Pharma's CEO for North America, Abhay Gandhi, has emphasized the potential impact of SEZABY on patients and their families.[24] As the first FDA-approved product for neonatal seizures, SEZABY provides a new treatment option that can make a meaningful difference in the lives of these patients. This achievement underscores the importance of research and innovation in healthcare.

FUTURE DIRECTIONS

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[25] which can be overcome by adapting gene therapy techniques, including gene replacement, gene silencing, and gene editing (e.g., CRISPR/Cas9). 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.[26] The annual treatment cost for a young child weighing 10 kg

Table 1: List of Orphan Drug Sponsored by India[19]

Generic name	Year in which designated	Orphan designation	Marketing approval	Sponsor company
Murine IgG1 monoclonal antibody binding to site II on G protein of rabies virus envelope and murine IgG2b monoclonal antibody binding to site III on G protein of rabies virus envelope	2019	Post-exposure prophylaxis against rabies virus infection.	No	Cadila Healthcare Limited, India
(3,5-Bis trifluoromethyl)-N-[4-methyl-3-(4-pyridin-3yl-pyrimidin-2-yl amino) phenyl] benzamide	2011	Treatment of chronic myelogenous leukemia.	No	NATCO Pharma Limited
4-Methyl-3-quinolin-3-ylethynylbenzoic acid N'-(2-chloro-6- methylbenzoyl) hydrazide	2019	Treatment of chronic myeloid leukemia	No	Sun Pharma Advanced Research Company Ltd.
4-[2-(3-Propyl-[1,2,4]0xadiazol-5-yl)-vinyl]-benzene-1,2-diol	2011	Treatment of chronic myeloid leukemia	No	Piramal Enterprises Limited
Flucytosine Injection for intravenous Infusion	2023	Treatment of cryptococcal meningitis	No	Cipla Ltd.
Humanized anti CD20 monoclonal antibody	2019	Treatment of Dermatomyositis	No	Biocon Limited
(3,5-Bis trifluoromethyl)-N-[4-methyl-3-(4-pyridin-3yl-pyrimidin-2-yl amino) phenyl] benzamideNRC-AN-019	2011	Treatment of Glioma	No	NATCO Pharma Limited
(R)-N2-(4-cyclopropyl-5-fluoro-6-methylpyridin-2-yl)-N4-(1, 5-dimethyl-1H-pyrazol-3-yl)-5-(3,4-dimethylpiperazin-1-yl) pyrimidine-2,4-diamine	2021	Treatment of malaria	No	Cadila Healthcare Limited
Phenobarbital sodium	2019	Treatment of neonatal seizures	Yes	Sun Pharma Advanced Research Company Ltd.
Heat killed mycobacterium w immunomodulator	2012	Treatment of non-small cell lung cancers that express desmocollin-3	No	Cadila Pharmaceuticals Limited
Autologous adult live cultured osteoblasts	2018	Treatment of osteonecrosis	No	Regrow Biosciences Pvt. Ltd.
Gemcitabine ready-to-use	2015	Treatment of ovarian cancer	No	Sun Pharmaceutical Industries Ltd.
Gemcitabine ready-to-use	2015	Treatment of pancreatic cancer	No	Sun Pharmaceutical Industries Ltd.
(3,5-Bis trifluoromethyl)-N-[4-methyl-3-(4-pyridin-3yl-pyrimidin-2-yl amino) phenyl] benzamide	2011	Treatment of pancreatic cancer	No	NATCO Pharma Limited
Anti-CEA Sheep-human chimeric monoclonal antibody labeled w/iodine-131 (KAb201)	2003	Treatment of pancreatic cancer	No	Avaant Pharmaceuticals India Ltd.
Nimodipine intravenous	2023	Treatment of subarachnoid hemorrhage	No	Cipla Ltd.

for some rare diseases in India might range from 18 lakhs to 1 crore 70 lakhs.[27] Repurposing existing drugs for new indications in rare diseases is a cost-effective strategy that can accelerate drug development timelines. The progression and impact of rare diseases are often not well understood due to the limited number of cases and which makes it difficult to identify and validate appropriate biomarkers for disease diagnosis and progression.[28,29] Which can be overcome by utilizing machine learning algorithms and big data analytics which can expedite the identification of disease mechanisms, biomarkers, and potential drug candidates. Global Collaboration and Regulatory Harmonization are orphan drug approval that can facilitate timely patient access to advanced therapies worldwide.

CONCLUSION

In India, further efforts are needed to enhance epidemiological research, raise awareness among health-care professionals and the public, and improve affordability and accessibility of orphan drugs. The landscape of orphan drug development and regulation in India is advancing, driven by initiatives such as the National Policy for Rare Diseases 2021 and regulatory reforms by the Central Drugs Standard Control Organization (CDSCO). These efforts, coupled with increased awareness, financial support, and research promotion, underscore a collective commitment to improving the diagnosis, treatment, and care of patients with rare diseases. The success of SEZABYTM by Sun Pharmaceutical Industries Limited exemplifies the transformative impact of orphan drugs, highlighting the potential of innovative research and collaboration. Looking ahead, emerging technologies such as gene therapy offer promising avenues for addressing rare diseases, but ongoing challenges such as limited data and high treatment costs persist. Global collaboration and regulatory harmonization will be crucial in ensuring equitable access to innovative therapies, fostering a future where every individual, regardless of the rarity of their condition, can benefit from improved health-care outcomes.

REFERENCES

1. Small Business Chronicles Newsletter; 2012. Available from: https://www.fda.gov [Last access on 2024 Mar 08].
2. Giannuzzi V, Conte R, Landi A, Ottomano SA, Bonifazi D, Baiardi P, *et al*. Orphan medicinal products in Europe and United States to cover needs of patients with rare diseases: An increased common effort is to be foreseen. Orphanet J Rare Dis 2017;12:64.
3. Rare Diseases: The Importance of Specialist Involvement in Diagnosis and Treatment – HealthOptions. Healthoptions.ai; 2023. Available from: https://healthoptions.ai/rare-diseases-the-importance-of-specialist-involvement-in-diagnosis-and-treatment/#:~:text=In%20the%20realm%20of%20rare%20diseases%2C%20specialists%20play [Last accessed on 2024 Mar 03].
4. Chatterjee P, Biswas T. Orphan drugs: A review of challenges and opportunities. Cureus 2021;13:e18617.
5. Prevalence and Incidence of Rare Diseases: Bibliographic Data. Available from: https://www.orpha.net/pdfs/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf [Last accessed on 2024 Mar 10].
6. CenterWatch. Facing Many Challenges, Orphan Drugs Take 18% Longer to Develop. CenterWatch. Available from: https://www.centerwatch.com/articles/12603-tufts-facing-many-challenges-orphan-drugs-take-18-longer-to-develop [Last access on 2024 Mar 16].
7. Srivastava G, Winslow A. Orphan drugs: Understanding the FDA approval process. In: Academic Entrepreneurship for Medical and Health Scientists. Pennsylvania: Perelman School of Medicine at the University of Pennsylvania; 2019.
8. Orphan Drug Credit. Investopedia. Available from: https://www.investopedia.com/terms/o/orphan-drug-credit.asp [Last access on 2024 Mar 16].
9. Moffett D. FDA Orphan Drug Designation for Rare Diseases. Nuventra. Available from: https://www.nuventra.com/resources/blog/orphan-drug-products [Last accessed on 2021 Aug 26].
10. Jesani A, Srinivasan S. New drugs and clinical trials rules, 2019: The market trumps ethics and participant rights. Indian J Med Ethics 2019;4:89-91.
11. Pharmaceutical Technology. India Issues New Clinical Trial Rules to Expedite New Drug. Available from: https://www.pharmaceutical-technology.com/pricing-and-market-access/india-issues-new-clinical-trial-rules-expedite-new-drug-html [Last access on 2024 Feb 02].
12. Ministry of Health and Family Welfare. Final NPRD; 2021. Available from: https://rarediseases.mohfw.gov.in//uploads/content/1624967837_final-nprd-2021.pdf [Last access on 2024 Apr 10].
13. Ministry of Health and Family Welfare. National Policy for Rare Diseases. New Delhi: Ministry of Health and Family Welfare; 2021.
14. Indian Council of Medical Research, GoI, Indian Rare Diseases Registry. Web Portal; 2017. Available from: https://bmi.icmr.org.in/irdr/index.php [Last access on 2024 Mar 05].
15. Bhattacharya S, Kotach VM, Majumder PP, Bhattacharya A. Rare diseases in India: Current knowledge and new possibilities. Proc Indian Nat Sci Acad 2016;82:1183-7.
16. Shaik A. National Rare Diseases Policy-India 2021: An Overview. ResearchGate; 2021. Available from: https://www.researchgate.net/profile/abdul-shaik-6/publication/359634683_national_rare_diseases_policy-india-2021-an_overview/links/6245eb2821077329f2e49782/national-rare-diseases-policy-india-2021-an-overview.pdf [Last access on 2024 Mar 29].
17. Rare Diseases in India: Time for Cure-Driven

Policy Initiatives and Action. ResearchGate; 2020. Available from: https://www.researchgate.net/publication/341830585_rare_diseases_in_indiatime_for_cure-driven_policy_initiatives_and_action [Last access on 2024 Apr 20].
18. Available from: https://www.pib.gov.in/pressreleaseiframepage.aspx?prid=1797759 [Last access on 2024 Apr 09].
19. Search Orphan Drug Designations and Approvals. Available from: https://www.fda.gov [Last access on 2024 Mar 05].
20. Sun Pharmaceutical Industries Limited. Sun Pharma Completes Acquisition of Concert Pharmaceuticals. Available from: https://sunpharma.com/wp-content/uploads/2023/03/press-release-sun-pharma-completes-acquisition-of-concert-pharmaceuticals.pdf [Last access on 2024 Mar 05].
21. Sun Pharma Launches SEZABY (Phenobarbital Sodium) in the U.S. Available from: https://www.sunpharma.com/wp-content/uploads/2023/01/press-release-sun-pharma-launch-of-sezaby™-in-the-us.pdf [Last access on 2024 Mar 20].
22. SEZABY Approved to Treat Seizures in Term and Preterm Infants. Available from: https://www.empr.com/home/news/sezaby-approved-to-treat-seizures-in-term-and-preterm [Last accessed on 2024 Apr 01].
23. Homepage. Sezaby. Available from: https://sezaby.com [Last accessed on 2024 Apr 01].
24. Sun Pharma. Sun Pharma Launches SEZABY (Phenobarbital Sodium) in the U.S. Available from: https://sunpharma.com/wp-content/uploads/2023/01/press-release-sun-pharma-launch-of-sezaby™-in-the-US.pdf [Last accessed on 2024 Apr 01].
25. Singh S, Pandey A, Vashisht R, Khanna T. Challenges and future directions of orphan drug development in India: A scoping review. Orphanet J Rare Dis 2022;17:92.
26. Patel P, Malhotra G, Gandhi P. Tackling rare diseases: Challenges and opportunities for orphan drug development in India. Indian J Med Ethics 2024;2:88-91.
27. Pharmatutor. Orphan Drugs in India and Challenges. Vol. 2. PharmaTutor; 2014. p. 84-9. Available from: https://www.pharmatutor.org/articles/orphan-drugs-in-india-and-challenges [Last access on 2024 Mar 26].
28. Datta-Mitra A, Gupta S, Balaji G, Singh A, Ganesan S, Daral S. Orphan drugs: Trends and issues. Perspect Clin Res 2019;10:147-53.
29. Applied Clinical Trials. Rare Diseases: Meeting Unique Challenges in Orphan Drug Development. Applied Clinical Trials. Available from: https://www.appliedclinicaltrialsonline.com/view/rare-diseases-meeting-unique-challenges-orphan-drug-development [Last access on 2024 Apr 09].

Source of Support: Nil. **Conflicts of Interest:** None declared.