REVIEW ARTICLE

UPI JOURNAL OF CHEMICAL AND LIFE SCIENCES (UPI-JCLS)

ISSN: 2581-4648 (An International online Peer Reviewed Open Access Journal)

www.uniquepubinternational.com Published by Unique Pub International (UPI)

A REVIEW ON ORPHAN DRUG DYNAMICS: TO TREAT RARE HEALTH CONDITIONS

Magasani Bala Narasimhulu*, J. Trinesh Sai, Ch. Lakshmi Narayanamma, Chandu Babu Rao

Priyadarshini Institute of Pharmaceutical Education and Research, 5th mile, Pulladigunta, Guntur-522017, Andhra Pradesh, India

***Corresponding Author**

Magasani Bala Narasimhulu

Received: 05 Mar 2025 Revised: 25 Mar 2025 Accepted: 26 Apr 2025

Abstract

Orphan drugs are pharmaceutical products designed to treat rare diseases, which affect a small percentage of the population. This article provides a detailed overview of orphan drugs, particularly focusing on the regulatory landscape, challenges, and ongoing initiatives in India. It examines the improvements in India's regulatory framework, including expedited review processes and exemptions from certain clinical trial requirements, aimed at facilitating the development and accessibility of orphan drugs. The article also highlights the contributions of Indian pharmaceutical companies in the orphan drug sector, showcasing a success story from Sun Pharmaceutical Industries Limited, which developed a significant orphan drug. Additionally, the article explores the challenges faced by India in orphan drug development due to its large population and limited resources, alongside the global advancements in gene therapy and drug repurposing. Despite the absence of a clear regulatory pathway for orphan drug development in India, recent policy changes indicate progress. The study advocates for a collaborative approach between the government, regulatory bodies, industries, and patient advocacy groups to accelerate the development of orphan drugs. Furthermore, it discusses the role of emerging technologies and business models in speeding up the process of creating novel treatments for rare diseases. The article also suggests that international collaboration and regulatory harmonization could improve access to these life-saving therapies, particularly in resource-constrained countries. With the continuous advancement of research and regulatory frameworks, there is hope for improving the treatment landscape for rare diseases globally, especially in countries like India.

Keywords: Bulgaria; cancer costs; health in equalities. Drug development; orphan drugs; patient advocacy Rare disease, Geneticdisorders Regulatory pathways.

Copyright:© 2025 The author(s). This article is licensed under a Creative Commons Attribution-NonCommercial4.0 International License.

INTRODUCTION

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 diagnosis, prevention, or treatment of a life-threatening or ently and severely disabling illness that affects no more than 5in 10,000EU citizens.[2] orphan diseases are rare conditions effecting only a small proportional of the population. They are called "orphan" diseases because they are often neglected by pharmaceutical companies and researchers, as they do not generate enough revenue to justify the cost of developing treatment strategies. Over 7000 orphan diseases effect an estimated 350 million people worldwide. Approximately 6000-8000 rare diseases have been identified to date, 80% of which are caused by mutations in numerous geans.

Rare diseases are those with low prevalence in the population. They are also known as orphan diseases, and the drugs developed against these diseases are known as orphan drugs. Despite being 'rare', rare diseases have been reported in 70–96 million individuals in India, 29 million in Europe, and 30 million in the US (Rajasimha *et al* .2014; Chakraborty *et al* .2022). In the US, the Congress passed the Rare Disease Actin1983.Through this act, the US Food and Drug Administration (US-FDA) has mandated regulatory processes and pathways for orphan drug development (Haffner 2016).Since then, several programs in the US have incentivized the development of orphan drugs (US-FDA2022). With the advent of modern technologies, some orphan drugs have seen the light of approval. In the past two years, the US-

FDA has approved *10 drugs belonging to advanced modalities such as gene therapy, gene-editing therapy, cell therapy, and gene-modified cell therapy (table 1) (Ciszewski2023; US-FDA 2023b). While these approvals have been exciting for the rare disease community, only10% of the *7000 rare diseases have any drug approved (Orphan-Drug-Approvals 2023; US-FDA 2023d; US- FDA 2023c).

BACKGROUND

Rare diseases, commonly referred to as orphan diseases, impact a small portion of the population.[3] There are approximately6,172 distinctive rare illnesses, 71.9% of which are inherited and 69.9% of which have only pediatric onset.[4] Despite their individual rarity, collectively, these diseases affect 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) which aims to encourage pharmaceutical companies to invest in research for these conditions by providing various benefits like market exclusivity and tax credits; essentially incentivizing the development of drugs that might otherwise be neglected due to low potential profit margins the world. The law was passed to encourage the development of drugs for rare diseases.

Brief overview and socio economic:

Whether a disease is rare or common, the primary objective of drug development is to develop a safe and effective treatment for the disease. Thus, regardless of the nature of the disease, the pathway for drug development involves common steps. The first step in the pathway involves understanding the pathogenesis of the disease Based on the disease biology, an appropriate drug is designed to prevent

The IND package of most global regulatory agencies consists of five chapters:

(i) the mechanism of action of the disease,
(ii) the process of product development and product characterization,
(iii) Pharmacology,
(iv) Toxicology
(v) The clinical protocol for conducting phase I of clinical trials.

Socioeconomic:

1. Economiccost

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.(5) Next generation sequencing, including whole exome and whole genome sequencing, is an established diagnostic tool used to reveal the genetic back ground of rare genetic disorders. However, its diagnostic yield is currently less than 50 an extremely low percentage of rare genetic diseases are currently curable with orphan drugs. Although a few orphan drugs have been developed to treat rare genetic diseases, many remain incurable. 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 un stability [6]. The development of drugs for rare genetic disorders is a complex and challenging process, and not all companies and successfully. Moreover, the prices of orphan drugs are relatively high compared to those of other drugs [7].

2. Strategies For Orphan Drugs

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 missingenzymes.ERT was first approved in the 1990s for Gaucher disease, and the first ERT drug replaced placenta derived glucerase, with imiglycerase in Chinese hamster ovary cells expressing recombinant human-β-gluco cerebrosidase. Subsequently, ERT drugs have been developed and approved for more than 10 LSD, including Fabry, Pompe, muco polysaccharidosis types I, II, IVA, VI, VII, and cholesteryl ester storage diseases(Table2).(8)In addition, LSD and ERT have recently been used in hypo phosphatasia with recombinant humanbone- targeted tissue- non-molecular strategy Specific alkaline phosphatase. Pegvaliase is an FDA-approved ERT used in adults with phenylketonuria (PKU) and uncontrolled blood phenylalanine concentrations.

3. Regulatory pathways for INDIA and US FDA:

The National Policy for Rare Disease 2021 and amendments adopted by India's Central Drugs Standard Control Organization (CDSCO) in 2019 mark important improvement 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 [9]. Orphan drugs are defined now as drugs used to treat diseases that affect fewer than500, 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 limitating the necessity for local clinical trials [10].

ORPHANDRUG: THEINDIANSCENARIOANDITSCHALLENGES

Table1. Strategy and examples of the diseases targeted for orphan drug development

Strategy	Exemplarydiseases	Product
Protein replacement therapy		
Enzyme replacement therapy	Gaucherdisease Fabrydisease MucopolysaccharidosisII	Imiglucerase Agalasidasebeta Idursulfase
Coagulation factor therapy	HemophiliaA	RecombinantfactorVIII
Small-molecule therapy		
Substrate reductiontherapy	Tyrosinemiatype1 Gaucherdisease Niemann-PicktypeC	Nitisinone Eliglustat Miglustat
Pharmacologicalchaperonetherapy	Fabrydisease Cysticfibrosis	Migalastat Ivacaftor
Cofactor therapy	Phenylketonuria	Sapropterindihydrochloride
Expression modification therapy	Sicklecellanemia	Hydroxyurea
Read-throughtherapy	Duchennemusculardystrophy	Ataluren
Monoclonalantibody therapy	Paroxysmalnocturnalhemoglobinuria Familialhypercholesterolemia X-linkedhypophosphatemicatemicrickets	Eculizumab Evolocumab Burosumab
ASOtherapy(exonskippingtherapy)	Duchennemusculardystrophy Spinalmuscularatrophy	PTC124 Nusinersen
Smallinterfering RNA therapy (Genesilencing therapy)	HereditaryATTRamyloidosis Acuteintermittentporphyria	Patisiran,Vutrisiran Givosiran
Genetherapy	LebercongenitalamaurosisduetoRPE65genemutation Spinalmuscularatrophy	Voretigeneneparvovec-rzyl Onasemnogeneabeparvovec-xioi
(Stem)celltherapy/Organtransplantation	Hurlersyndrome Ornithinetranscarbamylasedeficiency Hematologicmalignancies	Hematopoieticstemcelltherapy Livertransplantation ChimericantigenreceptorT(CAR-T)cell
Drugre purposing	Gaucherdisease Marfansyndrome	AmbroxolLosartan
mRNA therapy	Methylmalonicacidemia Phenylketonuria	Research
ATTR, amyloid transthyretin.		

Table2.Current status of approved enzyme replacement therapies for are diseases

Disease	Deficient enzyme	Product*	AvailableinKorea
Gaucherdisease	B Glucocerebrosidase	Imiglucerase(Cerezyme)	o
		Velaglucerasealfa(VPRIV)	o
		Taliglucerasealfa(Elelyso)	o
		Imiglucerase(Abcertin)	o
Fabrydisease	α-GalactosidaseA	Agalsidasaebeta(Fabrazyme)	o
		Agalsidasealfa(Replagal)	o
		Agalsidasebeta(Fabagal)	o
MPSI	α-L-Iduronidase	Laronidase(Aldurazyme)	o
MPSII	Iduronate2-sulfatase	Idursulphase(Elaprase)	o
		Idursulfasebeta(Hunterase)	o
MPSIVA	N-acetylgalactosamine-6-sulfatase	Elosulphasealpha(Vimizim)	o
MPSVI	ArylsulfataseB	Galsulphase(Naglazyme)	o
MPSVII	β-Glucuronidase	Vestronidasealfa(Mepsevii)	x
Pompedisease	Lysosomalα-glucosidase	Alglucosidasealfa(Myozyme/Lumizyme)	o
		Avalglucosidasealfa(Nexviazyme)	o
CESD	Lysosomalacidlipase	Sebelipasealfa(Kanuma)	o
Alpha-mannosidosis	Lysosomalα-mannosidase	Velmanasealfa(Lamzede)	x
CLN2	Tripeptidylpeptidase I	Cerliponasealfa(Brineura)	x
Niemann-PickdiseasetypeA/B	Acidsphingomyelinase	Olipudasealfa(Xenpozyme)	x
Hypophosphatasia	Tissue-nonspecificalkalinephosphatase	Asfotasealfa(Strensiq)	o
Phenylketonuria	Phenylalaninehydroxylase	Pegvaliase-pqpz(Palynziq)	x
MPS,mucopolysaccharidosis;CESD,cholesterylesterstoragedisease;CLN2,ceroidlipofuscinosistype2. *Brand name in parenthesis.			

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 (Ciszewski2023; SrivastavaandWislow 2023; US-FDA

2023c). 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 and it can be difficult to identify suitable patients for clinical trials. Take the drug for many years.

Table3.FDA/EM Aapproved gene therapy product forraremonogenic diseases

Disease	Product	Vector	Gene	Approach	Yearof approval
Lipoproteinlipasedeficiency	Glybera(alipogenetiparvovec)	AAV1	Lipoproteinlipase	Invivo	2012
SCIDduetoadenosinedeaminase deficiency	Strimvelis(GSK2696273)	Retrorviru s	Adenosinedeaminase	Exvivo(CD34 +cells)	2016
RetinaldystrophyduetoRPE65 mutation	Luxturna(voretigeneneparvovec-rzyl)	AAV2	RPE65	Invivo	2017
Spinalmuscularatrophy	Zolgensma(onasemnogeneabeparvovec -xioi)	AAV9	SMN1	Invivo	2019
β-Thalassemia	Zynteglo(betibeglogeneautotemcel)	Lentivirus	Modified β-globingene	Exvivo(CD34 +cells)	2019
Metachromaticleukodystrophy	Libmeldy(atidarsageneautotemcel)	Lentivirus	ARSA	Exvivo(CD34 +cells)	2020
Adrenoleukodystrophy	Skysona(elivaldogeneautotemcel/lenti-D)	Lentivirus	ABCD1	Exvivo(CD34 +cells)	2021
HemophiliaB	Hemgenix(etranacogenedezaparvovec)	AAV5	PaduavariantoffactorI X (FIX-Padua)	Invivo	2022

FDA/EMA,U.S.FoodandDrugAdministration/EuropeanMedicinesAgency;SCID,severecombinedimmunodeficiency;AAV,adeno-associatedvirus;ARSA,arylsulfataseA.

These programs include

(i) orphan drug designation;
(ii) Accelerated, fast-track designation of products;
(iii) Voucher programs (Srivastavaand.Wislow2023).

Since 1983, 6493 drugs with orphan drug designation have been in the development pipeline; of these, 700 have been approved by the US-FDA (Orphan-Drug-Approvals 2023; US-FDA 2023d).

In a Global-Genes conference in May 2023, Peter Marks, MD, the head of Center for Biologics Evaluation and Research (CBER), summarized the potential new developments in the regulatory pathways for orphan drugs (Marks and Wilson 2023). He emphasized there aspects of orphan drug development. First, the review and approval process of therapies should be streamlined and focused on platform strategies. For example, homogeneity of gene therapies using the same backbone viral vectors could be lever- aged in streamlining their approval process.

Current scenario of orphan drugs

The number of orphan drug clinical trials and approvals is increasing, but there are challenges to developing and using these drugs.

CLINICAL TRIALS

- The number of orphan drug clinical trials increased annually from 2013 to 2021.
- The number of phase I and phase II clinical trials increased annually from 2018 to 2021.
- Orphan drug approvals
- The number of orphan drug approvals has increased over time.
- Orphan drug policies
- The US has the Orphan Drug Act, which was passed in 1983 to encourage pharmaceutical companies to develop treatments for rare diseases.
- India has a National Policy for the Treatment of Rare Diseases (NPTRD).

FUTURE DIRECTIONS

Future directions in orphan drug research can en compass a wide range of innovative approaches. As approximately 80% of rare diseases are estimated to have a genetic origin[11] which can be overcome by adapting gene therapy techniques, including gene replacement, genes licencing 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 [12]. 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, 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.

CONCLUSION

Orphan drug development faces unique challenges due to the small patient population and high research costs, but recent advancements in genetic testing and gene therapies offer new hope for treating rare diseases. In India, the adoption of the National Policy for Rare Diseases has sparked progress, though more is needed to enhance accessibility and affordability. The success of drugs like SEZABYTM demonstrates the potential for innovative therapies to transform patient outcomes. Globally, governments incentivize orphan drug development through tax benefits, expedited approvals, and market exclusivity, helping to overcome the financial barriers faced by pharmaceutical companies. Ongoing collaborations between regulatory bodies, such as the US-FDA, and drug manufacturers are critical for advancing research and ensuring equitable access to these life-saving treatments. The market for orphan drugs is growing rapidly, expected to reach $340.84 billion by 2027, signaling a bright future for rare disease treatment innovation .Orphan drug development is a complex and costly process, primarily due to the limited patient population and the specialized nature of the diseases. In India, recent efforts, such as the introduction of the National Policy for Rare Diseases, have set the foundation for advancing the treatment of rare conditions.

AUTHOR CONTRIBUTIONS

All authors are contributed equally

FINANCIAL SUPPORT

None

DECLARATION OF COMPETING INTEREST

The Authors have no Conflicts of Interest to Declare.

ACKNOWLEDGEMENTS

None

REFERENCES

1. Gu M, Sun S, You Q, Wang L. Forward or backward: lessons learned from small molecule drugs approved by FDA from 2012 to 2022. Molecules. 2023;28(24):794. https://doi.org/10.3390/molecules28247941
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(1):1. https://doi.org/10.1186/s13023-017-0617-1
3. 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 J Rare Dis. 2021;16(1):265. https://doi.org/10.1186/s13023-021-01901-6
4. Rare Diseases: The Importance of Specialist Involvement in Diagnosis and Treatment. Health Options. 2023. https://doi.org/10.1111/cts.13619
5. Chatterjee P, Biswas T. Orphan drugs: A review of challenges and opportunities. Cureus. 2021;13(3):e18617. https://doi.org/10.22377/ajp.v18i3.5591
6. Orphanet. Prevalence and incidence of rare diseases: bibliographic data. Orphanet Report Series: Rare Diseases Collection. 2021;35. https://doi.org/10.1002/ajmg.a.61124
7. Center Watch. Facing many challenges, orphan drugs take 18% longer to develop. https://doi.org/10.1016/B978-0-323-90300-4.00060-4
8. IQVIA Holdings, Inc. Global use of medicines 2023 [Internet]. Durham (NC): IQVIA; 2023 [cited 2023 Mar 5]. https://doi.org/10.1377/hlthaff.2024.00469
9. Chiu ATG, Chung CCY, Wong WHS, Lee SL, Chung BHY. Healthcare burden of rare diseases in Hong Kong - adopting ORPHAcodes in ICD-10 based healthcare administrative data sets. Orphanet J Rare Dis. 2018;13(1):147. https://doi.org/10.1186/s13023-018-0892-5
10. Bloss S, Klemann C, Rother AK, Mehmecke S, Schumacher U, Mucke U, et al. Diagnostic needs for rare diseases and shared prediagnostic phenomena: results of a German-wide expert Delphi survey. PLoS One. 2017;12(2):e0172532. https://doi.org/10.1371/journal.pone.0172532

11. Liu P, Lupski JR, Yang Y. Reanalysis of clinical exome sequencing data. N Engl J Med. 2019;380(25):2478–80. doi:10.1056/NEJMc1812033
12. Rani CHU, Sumalatha G, Rao CHB, Varalakshmi TN. Alzheimer's disease - pharmacotherapeutic interventions. Int J Pharm Chem Sci. 2013;2(2). https://ijpcsonline.com/archives6/
13. Volmar CH, Wahlestedt C, Brothers S. Orphan diseases: state of the drug discovery art. Wien Med Wochenschr. 2016;167(9-10):197. https://doi.org/10.1016/j.drudis.2019.01.005
14. Yoo HW. Development of orphan drugs for rare diseases. Clin Exp Pediatr. 2023;67(7):315. https://doi.org/10.3345/cep.2023.00535
15. Gindi S, Methra T, Chandu BR, Boyina R, Dasari V. Antiurolithiatic and in vitro anti-oxidant activity of leaves of *Ageratum conyzoides* in rat. World J Pharm Pharm Sci. 2013;2:636–49. https://doi.org/10.1016/j.drudis.2019.01.005
16. Hwisa NT, Gindi S, Rao CB, Katakam P, Rao CB. Evaluation of antiulcer activity of *Picrasma quassioides* Bennett aqueous extract in rodents. Vedic Res Int Phytomedicine. 2013;1:27. https://doi.org/10.22377/ajp.v18i3.5591
17. 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. https://ijdra.com/index.php/journal
18. Rani CHU, Sumalatha G, Rao CHB, Varalakshmi TN. Alzheimer's disease - pharmacotherapeutic interventions. Int J Pharm Chem Sci. 2013;2(2). https://ijpcsonline.com/archives6/
19. Prasanthi G, Chandu BR, Pradeep Kumar Y, Swarnalatha D, Gopinath C. Chemical pharmacology of khat leaves. J Glob Trends Pharm Sci. 2014;5(4):2024–9. https://www.jgtps.com/admin/uploads/mw7QGy.pdf
20. Nama S, Chandu BR, Awen BZ, Khagga M. Development and validation of a new RP-HPLC method for the determination of aprepitant in bulk and pharmaceutical dosage forms. Trop J Pharm Res. 2011;10(4). https://www.ajol.info/index.php/tjpr/article/view/69565