Review Article
AMERICAN JOURNAL OF PHARMACY AND HEALTH RESEARCH
www.ajphr.com
2023, Volume 11, Issue 01
ISSN: 2321–3647(online)

Orphan Drugs: Advances in the Treatment of Rare Diseases

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ABSTRACT

Rare diseases are a major public health problem and public health challenge. Orphan drugs are medicines intended to diagnose, prevent, or treat life-threatening rare diseases. In a country like India, which is already struggling to provide basic healthcare facilities to its large population, it becomes very difficult for people living with rare diseases to access treatment options. The orphan drug legislation provides the pharmaceutical industry with a set of incentives and conditions to develop drugs for the treatment of rare diseases. The aim of this article is to describe orphan drugs for the treatment of rare diseases, Legislation, Indian Perspectives, Access to Orphan Medicines, Designation, Progress and Sales. Orphan drugs can help pharmaceutical companies reduce the impact of lost sales caused by blockbuster drug patent expirations. In our study we compare essential drugs with orphan drugs and examine approaches and future prospects in the development of orphan drugs.

Keywords: Rare Diseases, Orphan Drugs, Essential Medicines, Orphan Drug Act, NPRD, Advancements in Research.

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Received 11 January 2023, Accepted 4 February 2023

Please cite this article as: Shahi S *et al*., Orphan Drugs: Advances in the Treatment of Rare Diseases. American Journal of Pharmacy & Health Research 2023.

INTRODUCTION

Rare sicknesses are generally stated as 'orphan diseases'. The term is apt for many reasons. First, the term 'orphan' applies to children, associate degreed it happens that neonates, infants and kids are at highest risk for the foremost devastating rare diseases. Second, the construct of an 'orphan disease' implies an absence of stewardship for much too long, rare diseases were neglected by clinicians, medical researchers, the pharmaceutical industry, and society in general.[1]

According to World Health Organization (WHO), a rare disease is outlined as draining long disease or condition with a prevalence of ≤ one per one thousand population. Ultra rare sickness is outlined as that disease that includes lower than 2 patients per one hundred thousand populations. Totally different countries (developed and developing) have different definitions of rare disease according to suitableness of their own requirements. Attributable to this reason, non uniformity exists within the definition of rare disease and no accord exists amongst varied nations[2].

India, like several developing countries, presently has no commonplace definition. Considering the big population of India, we propose the threshold for a disease to be outlined as rare to be one in 5000, this is able to embody diseases that have a better prevalence, however don't have definitive therapy[3,5].

The exact number of rare diseases isn't known, but is calculable to be around 7000–8000 worldwide (Global Genes RARE Facts and Statistics). With the fast advances in genomic technologies within the last decade, the amount is increasing steady annually with new diseases and associated genes being discovered. Concerning 80% of rare diseases are genetic in origin, several of that are thought to be inheritable (Global Genes RARE Facts and Statistics).

Rare diseases additionally embody rare hereditary cancers, reaction diseases, innate malformations and infectious diseases amongst others. All rare diseases taken along have an effect on concerning 6–8% of the world's population[3,5].

Orphan medications are the merchandise supposed to treat rare diseases, so rare that sponsors are reluctant to develop them underneath usual promoting conditions. These products are developed to treat patients littered with terribly serious diseases that no treatment, or a minimum of a satisfactory one, has up to now been available[4].

Under "The New Drugs and Clinical Test Rules 2019", Orphan medication are outlined as a "drug supposed to treat a condition that affects less than 5 hundred thousand (500,000) persons in India.[5]

Orphan drugs is also defined as, drugs that don't seem to be developed by the pharmaceutical business for economic reasons however which reply to public health need. Actually, the indications of a drug may additionally be thought of as 'orphan' since a substance may be utilized in the treatment of a frequent sickness but may not have been developed for another, more rare indication[6].

Many orphans merchandise additionally secure government agency approval for non-orphan indications, products generally stated as "partial orphans." As of 2018, 23% of approved orphan medication also had non-orphan indications. Partial orphans are significantly common among drugs with the very best overall revenue[7].

ORPHAN MEDICINE LEGAL HISTORY

Several years of fundamental study are frequently required to uncover a material that is a good drug candidate during the development of a new drug. Animal investigations and clinical trials are conducted after that to gather information for examination and evaluation prior to the approval of a medicine. It's interesting to note that patient organizations acted as the primary impetus for the adoption of the orphan medication legislation, first in the USA and then in Europe[1].

Early in the 1980s, several rare disease patient organizations in the USA worked meticulously to draw attention to the lack of industry focus on the development of treatments for rare diseases. By utilizing various public relations strategies and collaborating closely with journalists, attention was finally brought to bear in the USA on this disease area. The orphan drug act was created when the US congress and senate discovered the enormous unmet medical need for patients[1].

Ronald Reagan signed the **Orphan Drug Act (ODA)** into law in 1983. The ODA's goal was to motivate and inspire the pharmaceutical sector to surmount the various obstacles to the development of orphan medications[1].

The **National Organization for Rare Diseases** was founded in 1983 by patient organizations that supported ODA (**NORD**). The rule on orphan medicinal products was approved by the European Parliament, Council and European Commission in December 1999. The European Commission approved the legislation in April 2000[1, 25].

(**EURODIS**) **European Organization for Rare Diseases**

THE ORPHAN DRUG ACT

The Orphan Drug Act was passed by Congress in 1983 to encourage the creation of medications for uncommon diseases. Due to the expectation that the pharmaceuticals would be unprofitable,

private sector had no motivation to invest in the development of treatments for tiny patient populations prior to the adoption of this historic legislation. Three incentives are provided by the law: (1) A tax credit of 50% of the cost of conducting human clinical trials, (2) A 7-year commercial exclusivity to sponsors of approved orphan goods, and (3) Federal research funding for the clinical testing of novel therapeutics to treat and/or detect rare diseases. When Congress granted companies creating orphan products an exemption from the typical medication application or "user" costs levied by the Food and Drug Administration in 1997, it created an additional incentive[8].

In 1984, 1985 and 1988, Congress modified the Act. Prior to submitting an application for marketing approval, sponsors were required by the 1988 amendment to request orphan classification.

The FDA oversees the Orphan Drug Act's administration and evaluates requests for orphan status. FDA claims that there is no doubt that the Orphan Drug Act has accelerated the development of medications for rare diseases. Over 1,000 orphan products have been recognized by the Office of Orphan Products Development since the law's passage; more than 200 of these have since achieved marketing approval. Many orphan medicines—including those licensed for multiple sclerosis, cystic fibrosis, and hemophilia—are regarded as ground-breaking treatments.

The biotechnology sector has benefited greatly from the Orphan Drug Act. Proteins, enzymes, antibodies, and other chemicals are used in biotechnology to treat illnesses[8].

By eliminating the prevalence-based definition of a rare disease, allowing other research fields to qualify as orphans, and reviving the FDA's original, albeit brief-lived, task of scrutinizing the demonstrable level of market neglect of the affected population, whether for reasons of rarity, poverty, gender, or other factors, policymakers can reclaim the ODA. As a tactic for gaining access to underutilized but socially significant health discoveries, waiting to see what comes down the pipeline and then seeking to negotiate better rates for orphan medications looks unlikely to be successful[9].

There are three main ODA "loopholes" that have been identified. First, drug companies have the option to "salami-slice" orphan status and approval for specific subsets of more prevalent disorders. Second, "mass market drug repurposing" refers to the practice of approving a medicine for an orphan indication after it has already received approval for a non-orphan ailment. The same legal incentives apply to repurposed orphans as they do to orphan medications that were initially developed to treat a rare disease. Third, each granted orphan indication grants a single

drug a new seven-year exclusivity period, which may "prolong market exclusivity" past a drug's patent term.[9,10]

INDIA'S PUBLIC HEALTH CHALLENGES INCLUDE RARE DISEASES

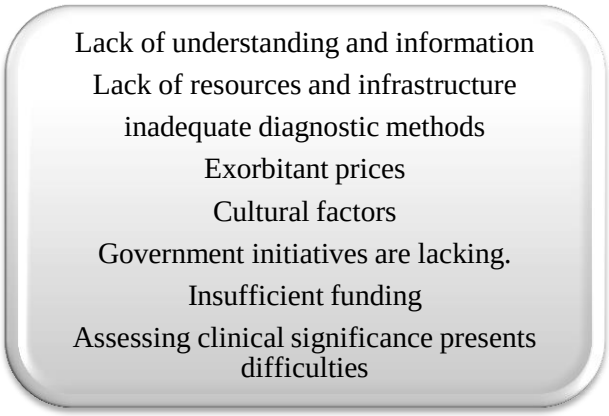
The field of uncommon diseases is developing and diverse, and it faces a knowledge gap in medicine and science. The landscape of rare diseases is systematically evolving as there are new rare diseases and conditions being noted and reported oftentimes in medical literature[11].

Globally conjointly as in India, rare diseases produce a very important challenge to public health systems in terms of – downside in grouping medical science data, that in turn impedes inward at burden of diseases and value estimations, problem in analysis and development, making correct associate degreed timely diagnosis, advanced tertiary level management involving long term care and rehabilitation and inconvenience and preventative value of treatment[11].

The Indian Rare Disease Registry was established by the Indian government in April 2017. 450 uncommon diseases have only been listed in the registry, according to information obtained from tertiary hospitals. There are an estimated 70 million people in India who are afflicted with a rare disease, despite the fact that there is no government data on this population (Kurian, Krishnan, and Sappani 2021). The start of rare diseases begins around 50% of the time at birth.[12]

Management of Uncommon Diseases In India: Unique Problems

In terms of public perception, diagnosis, treatment, and public policy related to rare diseases, India has various obstacles[3,4].



Current Indian Orphan Drug Development Status

In a convention hosted by the Indian Drug Manufacturing Association in November 2001, a group of pharmacologists recommended a unique legal framework for the development of orphan drugs in India to enact the "Orphan drugs act (ODA)", but nothing tangible has emerged as of yet[2].

An group, known as Organization for Rare Diseases India, has stepped forward to assist the patient population affected by rare illness conditions in order to meet the unmet health needs of Indian patients (ORDI; www.ordindia.org)[2].

ORDI Vision:

The goal at ORDI is to make it as simple as possible for Indians to diagnose and cure rare diseases. It would place a strong priority on gathering epidemiological data, igniting research, and promoting the establishment of registries and biorepositories[3].

ORDI Mission:

ORDI want to be the umbrella group that brings all of India's various disease-specific groups together and offers a common venue. Organization for rare illnesses India will develop plans of action on a range of issues pertaining to uncommon ailments, including epidemiology, natural history, disease processes, and therapeutics. It would look to the Indian government, including the DST, ICMR, DBT, CSIR, other government departments, and philanthropists, for support of these plans. Parent support groups, individual patients, different types of health professionals, hospitals (both public and private), corporate buildings, and pharmaceutical businesses will all be able to join[3].

Organizations From Throughout the World That Focus On Uncommon Diseases

Around the world, many groups are confronting the problem of uncommon diseases head-on. The names of a few of these organizations, along with their URLs, are listed alphabetically below[3].

- **CORD**: Canadian Organization for Rare Disorders (http://www.raredisorders.ca)
- **EURORDIS**: European Organization of Rare Diseases (http://EURORDIS.org)
- **GARD**: Genetic and Rare Diseases Information Center (https://rarediseases.info.nih.gov/GARD/)
- **HMDSN**: Hirschsprung's and Motility Disorders Support Network (http://www.hirschsprungs.info)
- **INOD**: In Need of Diagnosis (http://www.inod.org)
- **IRDiRC**: International Rare Disease Research Consortium (www.irdirc.org)
- **Jain Foundation** (http://www.jain-foundation.org/)
- **Madisons Foundation** (http://www.madisonsfoundation.org/)
- **NORD**: National Organization for Rare Disorders (http://rarediseases.org)
- **ORDR**: Office of Rare Diseases Research (http:// rarediseases.info.nih.gov)
- **Orphanet** (http://www.orpha.net)

- **RARE** – Rare disease, Advocacy, Research, Education (http://globalgenes.org/leadership)
- Rare Genomics Institute (**RGI**, USA) (http://raregenomics.org)
- **Rare Health Exchange** (http://rarehealthexchange. org)
- **SWAN**: Syndromes Without a Name (http://www. undiagnosed-usa.org)
- **Vascular Birthmarks Foundation** (http://birthmark. org)

In order to achieve the shared goal of finding answers to the issues of rare diseases and advocating for these people, ORDI will expand the work of these existing organizations in the field of rare diseases. In order to uncover probable causal mutations, ORDI and RGI USA have collaborated to establish a mechanism for enrolling patients and their families with unexplained disorders (suspected to be familial) in exome-sequencing projects. Other significant international organizations are being discussed by ORDI to see whether there is any potential for collaboration, and several of them have already established mutual cross-references.

Indian Organizations That Focus On Uncommon Diseases

The following is a list of some of the organizations and resources available to Indian patients with rare diseases[3].

- **ARDSI**–Alzheimer's and Related Disorders Society of India (http://www.alzheimer.org.in)
- **Birth Defects Registry of India** (http://www.fcrf.org. in/bdri_abus.asp)
- **Down Syndrome Federation India** (http://downsyndrome.in/)
- **Fragile X Society – India** (www.fragilex.org)
- **Genetic Alliance** (http://www.geneticalliance.org)
- **Hemophilia Federation** (http://www.hemophilia.in/)
- **Indian RETT Syndrome Foundation** (www.rettsyndrome.in)
- **Indian Association of Muscular Dystrophy** (www. iamd.in)
- **Indian Prader-Willi Syndrome Association** (http:// pwsindia.hpage.com)
- **IPSPI** – Indian Patients Society for Primary Immunodeficiency (www.ipspiindia.org)
- **LSDSS** – Lysosomal Storage Disorders Support Society (www.lsdss.org)
- **MERD** – Metabolic Errors and Rare Diseases (http://merdindia.com)
- **Muscular Dystrophy Association India** (http:// mdindia.org/)
- **Muscular Dystrophy Foundation India** (http:// www.mdfindia.org)
- **Muskaan** (intellectually disabled) (http://muskaandelhi.com/)

- **National Thalassemia Welfare Society** (http://www. thalassemiaindia.org/)
- **Pompe Foundation** (http://pompeindia.org/)
- **Rare Diseases India** (http://www.rarediseasesindia. org)
- **Retina India** (http://www.retinaindia.org)
- **Sjogren's India** (http://www.sjogrensindia.org)
- **Thalassemic India** (www.thalassemicsindia.org)

ESSENTIAL DRUGS vs. ORPHAN DRUGS

A comparison of essential drugs and orphan drugs[4]

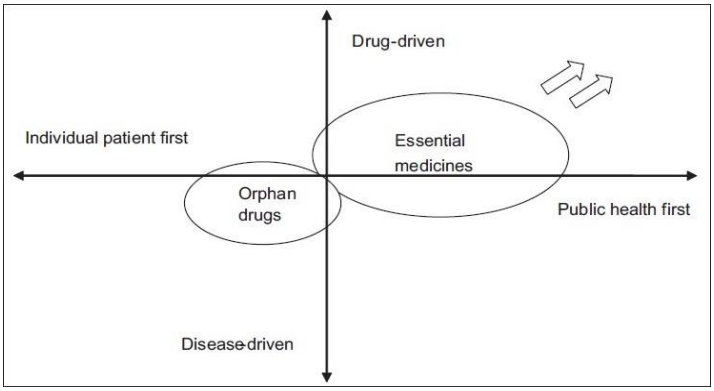


Figure 1 Essential Drugs vs. Orphan Drugs

Table 1: Essential Drugs vs Orphan Drugs

Aspect	Essential drugs	Orphan drugs
Concrete policies in place since	1977 worldwide	1983 in USA, 2000 in EU
Primary focus	Public health: bringing effective medicines to as many patients as possible	Individual patient: even a single patient warrants all possible treatment
Initiated and developed by	WHO, and Member States	Governments of Australia, EU, Japan and USA; patient groups
Criteria	Drug driven (i.e., drug to be listed on EML is efficacious, safe, cost effective, based on evidence-based data, etc.)	Disease driven (i.e., disease to be classified as an orphan drug has low prevalence <5–7.5: 10,000, is life-threatening, etc.)
Policies aim to	Provide established medicines to patients	Provide new medicines to as yet untreatable patients
Target populations	Initially low-income countries, now all countries	High-income countries, developed countries
Economics	Cost-effectiveness, sustainable, and affordable access	Relatively high prices per individual patient, cost-maximization per population

List of rare diseases[13]:

http://www.orpha.net/orphacom/cahiers/docs/G B/List_of_rare_diseases_in_alphabetical_order.

xlsx

Orphan Biological Products

Many orphan medications (in development) are produced via biotechnology from living organisms or are derived from them. A biopharmaceutical's 20-year patent period opens the market to less expensive variants of the drug known as biosimilars or follow-on biologics. Due to the challenges and expense associated with proving bio-similarity, orphan biopharmaceuticals typically face little competition from biosimilars.[14]

Access to Orphan Medicines

Before a drug is given marketing approval, regulatory bodies (the FDA and EMA) look at its characteristics to see if it has been proven to be both safe and effective in the target patient population. Orphan (and non-orphan) medications must therefore undergo further pricing and reimbursement procedures at the national level once MA has been approved[1].

Pricing and reimbursement are the two main factors that influence patients with rare diseases' access to orphan medications. Drug costs in Europe were on average 40% lower than those in the United States in 2008, with prices in Italy and Germany being respectively 55% and 70% of those in the United States[15].

Given that decisions regarding pricing and reimbursement are made decentralized, whereas decisions regarding the MA of pharmaceuticals are centralized. This is true for both orphan and non-orphan medications, although the hurdles for orphan drugs may be made more difficult by their greater cost and smaller datasets.

The size of the patient population needing therapy and the risk incurred to produce the product—which is reflected in the prospective return on investment—determine a drug's price and the related cost-per-patient in general. The cost to the patient will therefore be higher for higher-risk projects like research into rare diseases and orphan medications because they are more likely to need a higher potential return on investment in order to attract enough investor support. Incentives provided to the pharmaceutical industry through legislation to promote the development could be seen as a waste of money, which calls into question the idea behind drug legislation. If payers are not willing to reimburse treatment, this could have a serious negative impact on patients' access to desperately needed medications[1].

Due to the paucity of research on the pricing processes for orphan medications, the pricing of orphan drugs is frequently referred to as "black box" pricing. The cost of research and development must be recovered from a small group of patients, which makes orphan drug pricing special. Orphan medications are relatively expensive, frequently costing over €100,000

per patient per year, as a result of this, marketing exclusivity, and the lack of treatment alternatives.[16]

Orphan drug pricing follows the same economic logic as drug pricing generally: a producer sets the price of an orphan drug in an effort to cover research and development (R&D) expenses and to achieve a specific profit margin. In addition, the price considers market circumstances (such as the availability of alternative health technology), the regulatory pricing and reimbursement environment in a country, and the value of the product to the patient. But because of the market flaws that exist inherently in the orphan medicine market, prices are high for a variety of reasons[9,14]

We can estimate adjusted CETs corresponding to orphan and ultra-orphan medications by using estimates of variations in R&D expenses and treatment populations for orphan and non-orphans and by applying the suggestion of an acceptable pricing. The CET has been modified for medications with both a "ultra-orphan" designation and the "orphan" designation[17].

In many nations, decisions about pharmaceutical reimbursement (and/or pricing) are made using data resulting from economic analyses. The availability of sometimes insufficient and unreliable clinical data at the time of introduction hinders the economic evaluation of orphan medications. If clinical data are lacking, it has been suggested to permit increased use of substitute outcome metrics for orphan medications while enforcing a commitment to further study[14].

The most significant factor influencing patient access to orphan medications has long been thought to be insurance coverage and reimbursement for orphan medications. Due to their high cost, orphan medications that are not covered by insurance programmes are effectively inaccessible to patients. Even when they are, patient cost-sharing (via co-payments or coinsurance) can still place restrictions on their use. Health technology assessment (HTA), co-payments, post-marketing surveillance, and managed entry agreements are the four subthemes that make up this theme.[18]

Monopoly:

Marketing exclusivity is a powerful worldwide incentive for the development of orphan medications and grants a monopoly to the company. The lack of an alternative health technology for many orphan medications contributes to the monopolistic power. Marketing can also increase market dominance even further. Manufacturers are enticed to set the highest price for an orphan medicine that the market will bear in these circumstances. Patient access to orphan medications may be impacted by monopoly-based pricing strategies[19].

By dividing a condition into multiple sub-diseases that are considered rare diseases,

manufacturers can try to establish a monopoly (a strategy known as "disease sub-setting," "salami-slicing," or "disease stratification"). Examples of areas that are prime targets for the development of new rare diseases include oncology and pharmacogenomics. For a manufacturer, disease stratification may offer various advantages. The lack of "me-too" competitors due to marketing exclusivity and the tiny market make generic medications less profitable. Price increases when a medicine with a popular indication acquires a second, orphan indication are another example of how monopolistic market dominance affects prices[20].

INCENTIVES FOR ORPHAN DRUGS DEVELOPMENT

Table 2: Incentive and Grant Programs [21]

Incentive programs	Grant programs
For Pharmaceuticals for Uncommon Diseases	
Orphan Drug Designation Program	Orphan Products Grants Program (Clinical trials & Natural history studies)
Rare Pediatric Disease Priority Review Voucher Program	Pediatric Device Consortia (PDC) Grants Program
Humanitarian Use Device (HUD) Program	Rare Neurodegenerative Disease Grants Program

Table 3: Incentives for Orphan Drug Development in US, EU and Japan [15, 25, 31]

	United States	European Union	Japan
Implementing agency	USFDA OOPD (Office of Orphan Products Development)	Committee for Orphan Medicinal Products in European Medicines Agency (EMA)	Ministry of Health and Welfare 31
Monetary encouragement	Up to 50% of tax credit in clinical development cost Waiving of user fee for application of MAH.	Fee reduction, varies from time to time. Tax relief, price and reimbursement incentive to MAH.	Waiver of user fee Tax credit: up to 15%-20% (decided on case-to-case basis) Financial subsidies
Legislation	Orphan disease act rare disease act	Regulation(EC) No 141/2000	
Marketing exclusivity	7-year marketing exclusivity	The 10-year market exclusivity	Ten-year extension on reexamination of marketing authorization
Scientific assistance in drug development plan	Free scientific guidance by FDA.	Free protocol assistance	Free reduction up to 30% for scientific assistance (protocol).
Different orphan drug development programs	The FDA Orphan Products Grant Program and other programs	Research grant by European Commission	Research grants (NIBIO, AMED)
Priority review	Yes	Yes	Yes
Fast approval process	Yes	Yes	Yes
Regulatory mechanisms to speed up orphan drug certification and approval process	Breakthrough designation	Centralized procedure	Price control
Pre-licensing access	Yes	Yes	
Scientific advice (Protocol assistance)	Yes	Yes	Yes

Drug Designation as An Orphan

Products that the FDA has concluded could be used to treat a rare disease are given "orphan designations". Products that the FDA has concluded are prepared for commercialization in the United States are given "orphan approvals.

The Office of Orphan Products Development oversees the FDA's small grants program and grants designations. The awards help fund clinical studies examining the efficacy and safety of treatments for rare diseases. Applications for marketing approval are examined by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER)[8].

Orphan designations are frequently based on two criteria: severity (life-threatening or persistently debilitating illnesses), and unmet need (new product delivers significant clinical benefit or there is no alternative therapy). This foundation is frequently further divided into economic or prevalence criteria[25].

Sponsors must submit an application to the Office of Orphan Products Development using the FDA Form 4035 that includes information on the rare disease for which the drug will be studied, the precise indication for the drug, a description of the drug, proof of the prevalence of the disease, and the regulatory and marketing status and background of the product. Although it is the Office's policy to respond to requests for orphan designation within 60 days of receiving them, this may not always be possible if the Office requires more information from the sponsor. If the drug performs well in clinical trials and is found to be safe and effective after acquiring the orphan designation and additional study, a sponsor may apply for marketing authorization. The CDER and CBER make the official decisions regarding whether to approve a drug; the office has no say in these matters.[21]

From a high of 267 days in 1996, the average time the Office of Orphan Products Development needs to designate a product fell to 160 days in 2000[8].

There are many advantages for businesses committed to developing orphan drugs. For instance, the classification of an orphan medication in the EU grants the approved product ten years of commercial exclusivity, compared to seven years in the US[22].

Additionally, obtaining orphan drug status entitles businesses to protocol help from regulatory agencies as well as potential access to several fast approval procedures. Additional advantages include waived or reduced regulatory fees, as well as the possibility of tax rebates and subsidies for clinical studies with rare diseases in the US.

Common Misunderstandings Surrounding the Designation of Orphan Drugs

1. The orphan designation is a requirement for approval.
2. Each indication can only have one orphan designation.
3. To be designated as an orphan medicine, a medication must be deemed to be both effective and safe.
4. The application process for orphans is difficult.
5. Applications from the US and the EU must meet the same designation requirements.
6. Examining orphan designations has remained constant over time.
7. The only advantage of the orphan approval is the seven-year exclusivity.[21,23]

Common Problems In Orphan Drug Development Are Addressed By New FDA Guidance Guidance:

- "Adequate description and understanding of the disease's natural history
- Adequate knowledge of the disease's pathophysiology and the drug's proposed mechanism of action
- Considerations in nonclinical pharmacotoxicology to support the proposed clinical investigation or investigations
- Reliable endpoints and outcome assessment
- Standard of evidence to establish safety and effectiveness data; and
- Considerations in drug manufacturing during drug development[24]."

The advice goes on to explain the FDA's standards and flexibility for taking into account evidence of efficacy and safety, and it also has a section on chemistry, manufacturing, and controls that is specifically tailored to problems with medications used to treat uncommon disorders.

The National Policy on Rare Diseases

The Central Government released the National Policy on Rare Diseases for the first time in 2017. The 2017 National Health Policy emphasizes the importance of managing rare/orphan diseases. The policy was suspended due to difficulties in execution. Lack of transparency regarding cost-sharing, disease coverage, and patient eligibility for receiving treatment for the rare disease under this insurance were some problems with the policy, as stated by the States. In March 2021, the Ministry of Health and Family Welfare officially authorized the publication of the revised National Policy on Rare Diseases. The new policy does not yet have a strong framework with procedures that might make treatment affordable and accessible for the average person, despite addressing the shortcomings of the previous policy by providing guidelines regarding which scheme of the central government to operate under and other clarifications[11, 12.]

The government-appointed committees provided a number of suggestions for the creation of a "national policy for treatment of uncommon diseases." The recommendations extend beyond the provision of treatment funding and adopt a more comprehensive approach to rare diseases, including suggestions for prevention, raising public awareness, imparting knowledge, conducting research and development in diagnosis and treatment, developing and producing drugs for rare diseases at competitive prices, offering insurance coverage, etc[11].

In order to create a database of rare diseases in India, the ICMR established a National Registry in 2017. According to the policy, nine institutes should be designated as Centers of Excellence, serving as top tertiary hospitals with resources for the diagnosis, treatment, and prevention of uncommon diseases. Similar to this, the establishment of five Nidan Kendras is recommended to conduct rare disease screening, testing, and counselling, as well as to provide treatment if the necessary infrastructure is in place. The program largely relies on health care professionals to conduct screening activities for the early diagnosis of diseases in order to provide coverage over the entirety of India[5,12].

The policy does not clearly define the need for cooperation at the various levels amongst the institutions of all stakeholders. There is no clear method in the policy to address problems with service delivery[12].

The main goal of national plans for rare illnesses is to establish a legal framework for patient advocacy, access to services, treatment, and information, as well as research stimulation. Cross-border regulation is particularly crucial in the context of rare diseases since domestically unavailable orphan medications, specialized specialists, and treatment facilities frequently prevent patients from receiving treatment[25].

The National Policy of Rare Diseases, 2021 increased the financial assistance for patients with rare diseases from Rs. 20 lakhs to Rs. 50 lakhs under the umbrella plan of Rashtriya Arogya Nidhi (RAN), according to an office memorandum released by the Union Health Ministry on May 19 2022[5].

Creating Coordinated Policies for Orphan Pharmaceuticals:

Several hundred rare diseases are listed in a recent report by Orphanet, and the majority of policy discussions within the European Union focus on actions that should be taken to advance the development and accessibility of drugs for rare diseases as a group rather than the relative importance of different rare diseases. However, the Institute of Medicine in the USA emphasized that systems for balancing research priorities would be a significant element of the overall approach when discussing possibilities for advancing research and development in rare diseases.

The indication to manufacturers that those drugs deemed higher priority would be more likely to be paid, if produced, would be provided if the priorities were made more clear. Given the small number of potential patients per nation and the fact that pharmaceutical corporations make their research decisions on a global scale, the second aspect of "joining up" policies would be enhanced international government cooperation[26].

ORPHAN DRUGS: CLINICAL TRIALS

Orphan Drugs: A New Business Potential

In comparison to non-orphan medications, the economic and investment justification for developing and commercializing orphan drugs appears to be stronger. Given the lower target patient populations for orphan illnesses, this is impressive. The advantageous economics for orphan medications could be explained by a number of factors. Clinical trials for orphan pharmaceuticals can be completed faster than those for non-orphan drugs (3,9 years as opposed to 5,4 years), and regulatory submissions for orphan drugs have a higher success rate (93% as opposed to 88%) [1]

The two main distinctions between orphan and non-orphan drugs are that (i) the costs of research and development are probably lower for orphan drugs due to the less extensive clinical development program, and (ii) the treatment populations for orphan drugs are probably smaller due to the rarity of the disease[17].

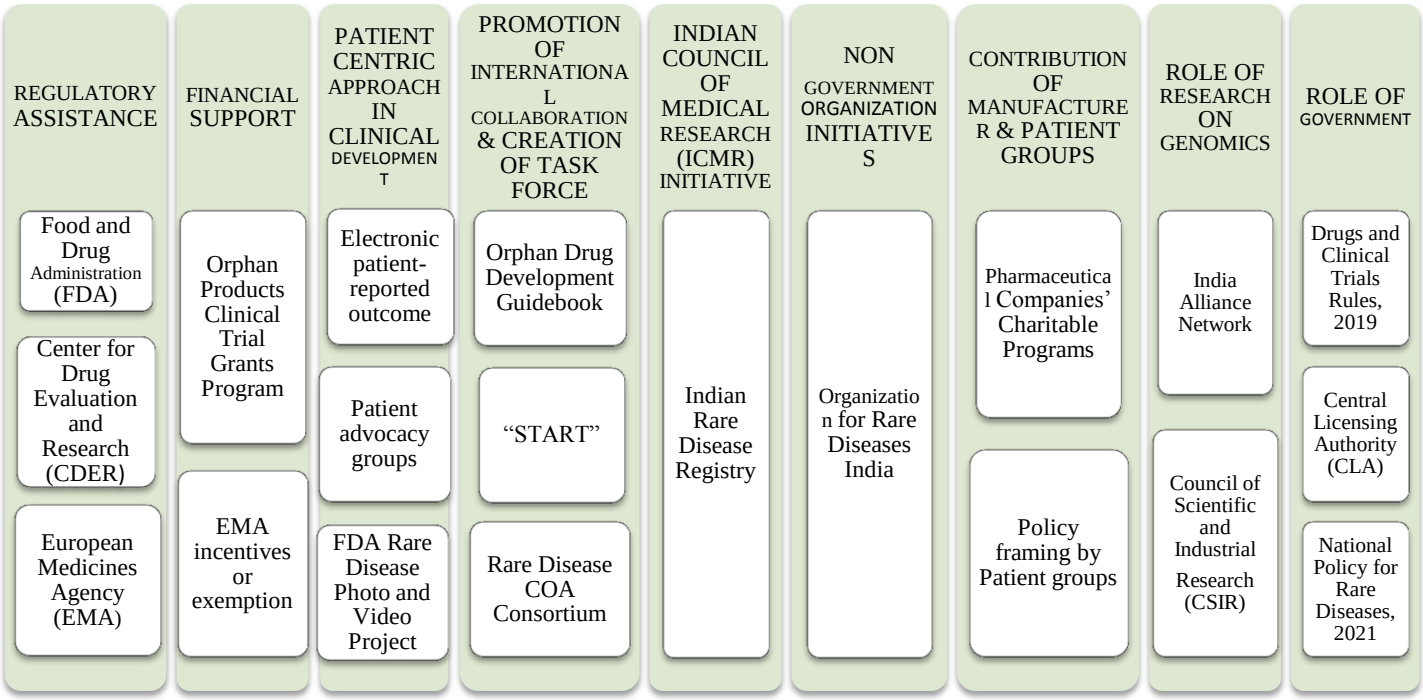
The "economics and investment case for orphan drug development" was judged to be "more beneficial than for non-orphan pharmaceuticals" by a study (Meekings, Williams, and Arrowsmith 2012). Therefore, creating treatments for rare disorders yields larger profits for pharmaceutical corporations than creating medicines for prevalent illnesses[12].

Clinical Trials

Clinical trials involving orphan pharmaceuticals demand greater work than regular trials do. The source of funding is a significant problem when carrying out such experiments. For any such trial, the funding may come from the government or from the pharmaceutical business. Clinical trials involving orphan pharmaceuticals must also be conducted in well-equipped laboratories with trained staff, which adds still additional challenge to carrying out these kinds of trials. A small sample size resulting from fewer patients may also present challenges for researchers, making it very challenging to generalize findings to the wider population[2]. There are several extra challenges that must be overcome during orphan drug clinical trials, according to several authors. Complex logistical issues, ethical concerns, disease heterogeneity in manifestation and fluctuation in severity, limited understanding of disease natural history, lack of accepted clinical

efficacy outcome measures, absence of a minimum threshold for clinical significance, validation of biomarkers, and lack of animal models for rare diseases are a few of them.[27] Carefully selecting the trial design could assist to address some of these problems. Additionally, as long as they are logical, regulatory agencies are adopting new trial designs[22].

ADVANCEMENTS IN ORPHAN DRUG RESEARCH RECENTLY[28]



RISE IN SALES OF ORPHAN MEDICATIONS

With a 12% CAGR from 2021 to 2026, the orphan medicine market will grow more than twice as quickly as the non-orphan market. 20% of all prescription medicine sales by 2026 will come from orphan drug sales[29].

Vertex Pharmaceuticals was the company that relied the most on orphan medications among those that commercialized them in 2021. In actuality, orphan medications were the sole source of Vertex's sales earnings. By 2026, it is predicted that this ratio would only slightly decline to 98 percent. The global orphan medicine business has expanded to varied degrees despite the price and variety of treatments offered[30].

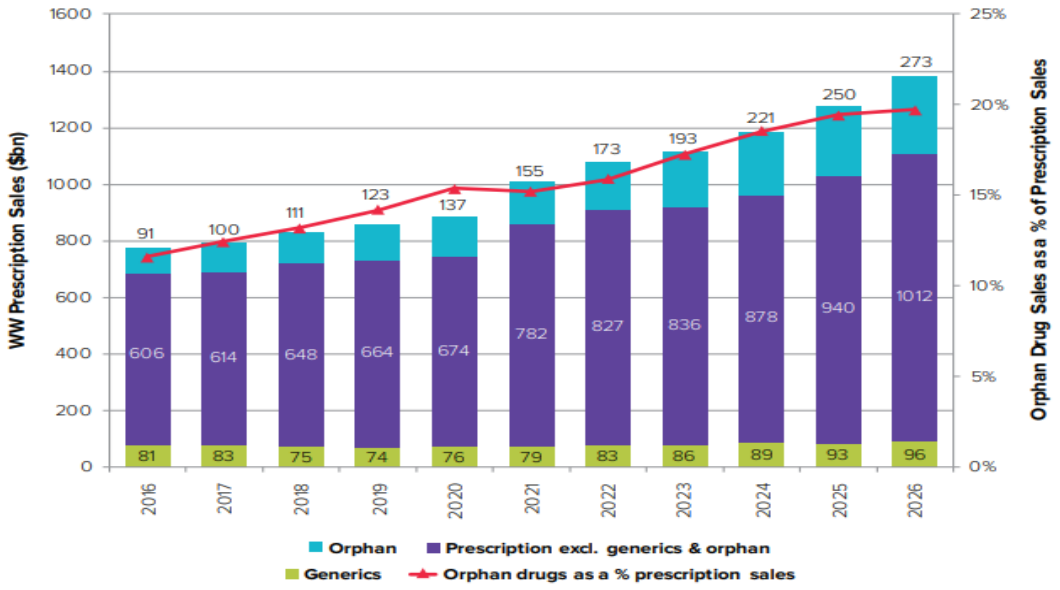


Figure 2: Worldwide Orphan Drug Sales & Share of Prescription Drug Market (2021/2026)

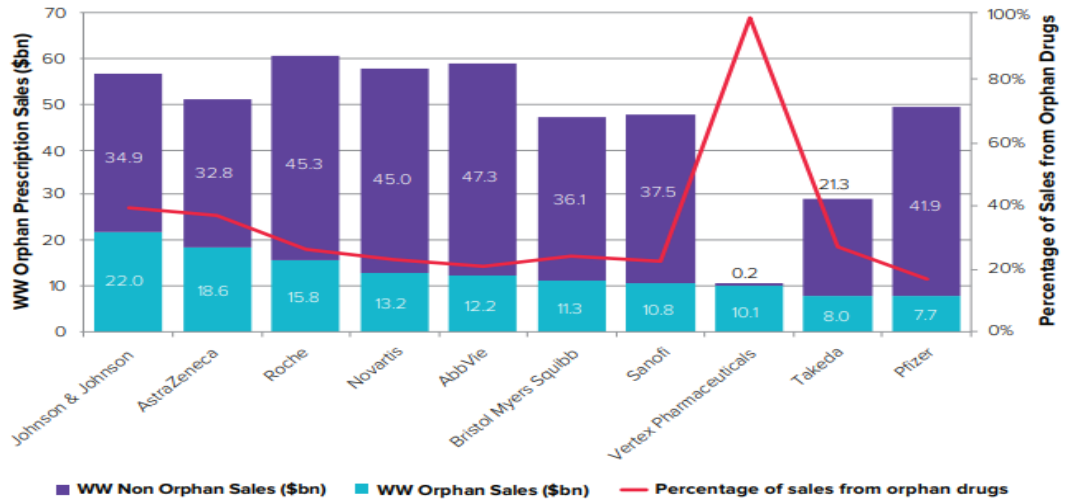


Figure 3: Worldwide Orphan Drug Sales (2021/2026): Top 10 Companies & Total Market[29]

Top 10 Orphan Drugs Sold Worldwide[29]

1. Imbruvica {AbbVie & Johnson & Johnson}
2. Darzalex {Johnson & Johnson}
3. Trikafta {Vertex Pharmaceuticals}
4. Hemlibra {Roche & Chugai Pharmaceutical}
5. Lynparza {AstraZeneca}
6. Jakafi {Incyte & Novartis}
7. Ultomiris {AstraZeneca}
8. Venclexta {AbbVie}

9. Calquence {AstraZeneca}
10. Vyndaqel {Pfizer}

5 Leading Orphan Startups Affecting the Pharmaceutical Sector[31]

Table 4: Five leading Orphan Startups

Startup Name	Drugs	For Disease Treatment
Tiburio Therapeutics	*TBR-065, TBR-760*	Rare Endocrine Diseases
Versantis	*VS-01*	Acute Liver Diseases
MeiraGTx	*AAV-CNGB3,AAV-CNGA3*	Achromatopsia
Dynacure	*DYN101*	Centronuclear Myopathies (CNM)
Belite Bio	*Anti-RBP4, LBS-008*	Age-Related Macular Degeneration (AMD)

FURTHER PERSPECTIVES

Due to inadequate diagnosis and treatment, rare diseases need increased attention. Rare disease treatment and prevention are seen as "no man's land.[32]"

Compared to larger rare illness foundations, smaller rare disease groups are less well-known. As a result, the case of ultra-rare disease is a significant concern that is also connected to the lack of universal criteria. A illness that affects fewer than 2000 people is considered an ultra-rare orphan disease in the USA. As a result, it is anticipated that in the future an internationally recognized definition for extremely rare diseases will be developed and that orphan legislation would be updated to reflect the unique requirements of patients[33].

The procedure for gaining access to markets is another significant obstacle. The process is quite complicated because there is no uniformity of the evaluation and several methodologies are employed. The EC's EUnetHTA initiative and the CAVOMP model, which promote understanding and shared methods to economic evaluations, could both be highly helpful in overcoming obstacles in the decision-making process for reimbursement[34].

In addition to raising public awareness of rare diseases, groups like EURODIS are also persuading governments to pass laws that will improve the quality of life for these unique people. The 29th of February has been designated as "the rare illness day" by EURORDIS and National Alliances in honor of notable individuals who are afflicted by rare diseases[35].

Precision medicine is going to be pushed into rare disease clinics all over the world as a result of the recent epochal improvements in drug discovery, diagnostics, and regulatory paradigms[3]. Since biologics make up more than 50% of the orphan medicine market, the arrival of biogenetics will have a significant impact on the industry's future[4].

Precision diagnostics for rare diseases are projected to benefit from the worldwide rapid expansion and breakthroughs in molecular diagnostics and bioinformatics. The development and democratization of precision diagnostics for rare diseases will greatly benefit from India's strengths in information technology and bioinformatics[3].

Due to its natural skills in drug and vaccine development and manufacturing, India has a significant potential to develop and manufacture biologics, small molecule medicines, and vaccinations for uncommon diseases at a low cost. Particularly in the generic market segment, Indian pharmaceutical companies are widely known for their capacity to develop and manufacture small molecule drugs[3].

To develop medications for rare diseases, we need significant industrial and regulatory backing. Collaboration between business and academia is also significant[2]. Depending on the R&D investment, the return on such investment, the tax and patent incentives, and the regulatory policies of the country, an effort should be made to generate significant pharmaceuticals for the benefit of the entire globe. Acceptance of these ideas could result in positive shifts in national perceptions and stop the "orphanization of innovative medications[4]."

CONCLUSION:

Rare sicknesses are generally stated as `orphan diseases. Under “the New Drugs and clinical test Rules 2019”, Orphan medication are outlined as a “drug supposed to treat a condition that affects less than 5 hundred thousand (500,000) persons in India”. The Orphan Drug Act was passed by Congress in 1983 to encourage the creation of medications for uncommon diseases. Globally conjointly as in India, rare diseases produce a very important challenge to public health systems in terms of – downside in grouping medical science data, that in turn impedes inward at burden of diseases and value estimations, problem in analysis and development, making correct associate degreed timely diagnosis, advanced tertiary level management involving long term care and rehabilitation and inconvenience and preventative value of treatment. Pricing and reimbursement are the two main factors that influence patients with rare diseases` access to orphan medications. Clinical trials involving orphan pharmaceuticals must also be conducted in well-equipped laboratories with trained staff, which adds still additional challenge to carrying out these kinds of trials. Due to its natural skills in drug and vaccine development and manufacturing, India has a significant potential to develop and manufacture biologics, small molecule medicines, and vaccinations for uncommon diseases at a low cost. To develop medications for rare diseases, we need significant industrial and regulatory backing. Collaboration between business and academia is also significant.

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