"Regulatory Aspects and Global Perspectives on Orphan Drugs and Rare Diseases: Challenges, Incentives, and Future Directions"

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Abstract

This project about the regulatory framework for orphan drugs, focusing on policies and guidelines established by agencies like the FDA and EMA. It explores incentives for pharmaceutical companies, such as tax credits and market exclusivity, and the challenges faced by stakeholders. The project aims to balance regulatory standards, scientific innovation, and patient access by analyzing case studies of orphan drug approvals. It also assesses the effectiveness of current regulatory strategies in promoting orphan drug development while ensuring safety, efficacy, and affordability for rare disease patients.

Keywords: Orphan drugs, Regulatory framework, Orphan Drug Act, Post-marketing surveillance, India orphan drug policy, Gene therapy.

Introduction

A medicinal product designated as an orphan drug is one that has been developed specifically to treat a rare medical condition referred to as “orphan disease.” It may be defined as drugs that are not developed by the pharmaceutical industry for economic reasons but which respond to public health need[1]. Orphan drugs are medications developed specifically for rare diseases or conditions, which affect a small percentage of the population (typically fewer than 200,000 individuals in the U.S. or less than 5 in 10,000 people in the EU).Orphan drugs (OD) are pharmaceutical agents developed for treating rare medical conditions. The Kefauver-Harris Bill (1963) requires all drugs to be proven safe and effective before approval for the US market. In India, only 38 would-be orphan drugs were approved by FDA before the 1983 Act. The US Food and Drug Administration (US-FDA) has mandated regulatory processes and pathways for orphan drug development, and 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[2].

In India, although some guidance for clinical trials of orphan drugs has recently been published, an overall pathway for orphan drug development does not exist due to several challenges ranging from insufficient financial investments to inadequate scientific and technical resources. Challenges include lack of patient registries, insufficient patient recruitment, insensitive clinical endpoints, and lack of biomarkers. This report reviews recent advances in the US regulatory pathways for orphan drug development and provides insights on the current scenario regarding orphan drug development in India. It also proposes a step-wise approach for drug developers and regulatory authorities to draft a regulatory pathway for orphan drug development in India[3].

Overview of orphan drugs and Rare disease

"Orphan Drugs" - Denotation in various countries

United States: As defined in the United States, any drug developed under the Orphan Drug Act of January 1983 (ODA) is an orphan drug. The ODA is a federal law concerning rare diseases (orphan diseases) that affect fewer than 200,000 people in the United States or are of low prevalence (less than 5 per 10,000 in the community)[1].

Europe: A disease or disorder that affects fewer than 5 in 10,000 citizens is the definition for rare in Europe (Orphan Drug Regulation 141/2000). At first glance, this may seem a small number, but by this definition, rare diseases can affect as many as 30 million European Union citizens. According to EURORDIS (European Organization for Rare Diseases), the number of rare diseases numbers from about 6,000 to 8,000, most of which have identified genetic conditions, with medical literature describing approximately five new rare conditions every week[1].

Japan: A drug must meet the following three conditions to be considered for orphan drug designation in Japan. Any disease with fewer than 50,000 prevalent cases (0.4%) is Japan's definition of rare. The drug treats a disease or condition for which there are no other treatments available in Japan, or the proposed drug is clinically superior to drugs already available on the Japanese market. The applicant should have a clear product development plan and scientific rationale to support the necessity of the drug in Japan. Once clinical trials are completed, a New Drug Application (NDA) can be submitted. It is important to keep in mind that while Japan has orphan drug legislation, this legislation has room for interpretation. The MHLW (Ministry of Health, Labour, and Welfare) makes orphan drug designation and approval decisions on a case-by-case basis. This is especially true when determining the number of Japanese clinical trials required for approval[2].

India: The need for such an act is thus evident from the initiative by the Indian Pharmacists and the Government to implement Laws, which would strengthen the health infrastructure and provide relief to the numerous rare disease sufferers throughout the country. A group of pharmacologists at a conference held by the Indian Drugs Manufacturers Association in 2001 requested the Indian Government to institute the Orphan Drug Act in India[2].

The Orphan Drug Act, 1983

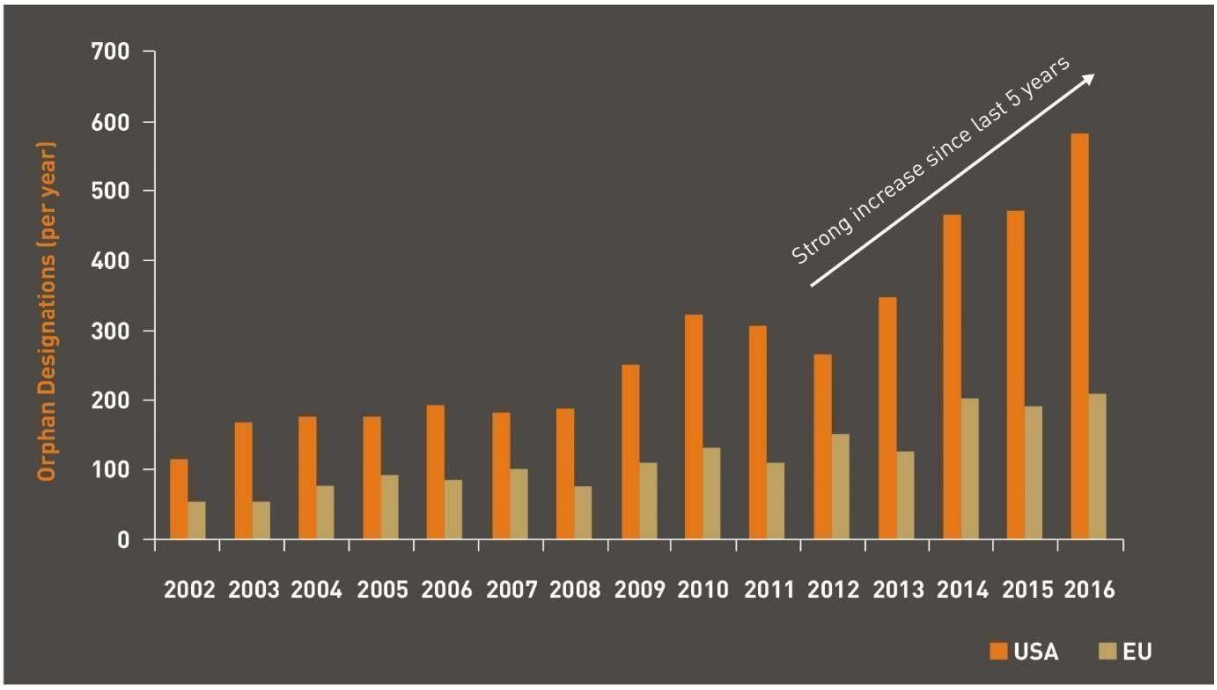
The political and social climate that followed the thalidomide disaster in the late 1950s directly led to the implementation of the US Drug Act. The 1962 Kefauver-Harris amendments significantly raised the expense of medication development by requiring pharmaceutical companies to prove their therapeutic efficacy and innocuity. The pharmaceutical industry concentrated on huge illness populations in order to increase profits[4].

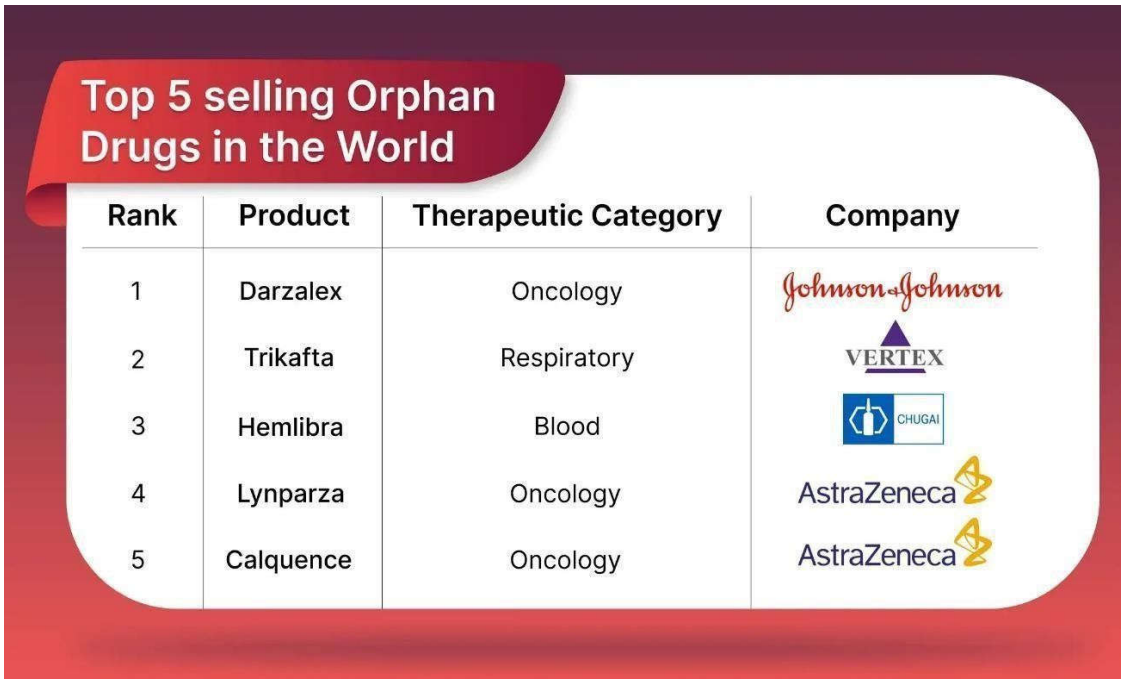
whereas smaller communities of rare diseases were "orphaned". Public pressure influenced political thinkers and health policy in the late 1970s, and NGOs like the National Organization for Rare Diseases brought attention to the predicament of people with rare diseases. In 1983, President Ronald Reagan signed the Orphan Drug Act (ODA) into law with the intention of promoting research into rare diseases and the creation of pharmacological medicines for the treatment of unusual disorders.

In contrast, rare disease populations were "orphaned" . In the late 1970s, NGOs such as the National Organization for Rare Diseases raised awareness of the plight of individuals with rare diseases, and public pressure impacted political thinkers and health policy . In order to encourage research into rare diseases and the development of pharmaceutical medications for the treatment of uncommon conditions, President Ronald Reagan signed the Orphan Drug Act (ODA) into law in 1983[3].

year market exclusivity for orphan drugs; tax credits total in half of development costs; research and development grants; fast-track development and approval; access to Investigational New Drug Program and pre approval; waived drug application fees . Orphan drug status is granted through the FDA and is independent of the patent system .In addition, orphan drug market exclusivity periods come into effect at the date of market approval and are not expended during product development .With over 2000 orphan designations and an excess of 300 currently approved orphan drugs, the US Orphan Drug Act appears highly successful. Nonetheless, the current political, social and economic context has evolved over the 25 years since its implementation. Mean patient populations for orphan diseases are consistently rising and technological advances forecast an era of personalised medicine. According to the National Institutes of Health, a total of 6819 rare diseases are presently registered in the United Sates These diseases afflict an estimated 20–25 million Americans and approximately 250 new rare diseases are described annually .Manufacturers are increasingly interested in orphan designation as orphan drugs often face less competition and are more likely to demonstrate[13].

Figure 1: U.S. and EU Orphan Designations Granted Every Year (2002-2016)





Fig; 2. Top 5 Selling orphan drug in world

List of Rare Diseases and Orphan Drugs[1]

Sr. no.	Trade name	Generic name	Company	designation
1	Azedra	Iobenguane I 131	Progenics Pharmaceutical Pvt.Ltd	Treatment of neuroendocrine tumors.
2	Omegaven	Omegaven emulsion	Fresenius Kabi USA	Treatment of parenteral nutrition associated liver disease.
3	Signifor	Pasireotide	Novartis Pharmaceuticals Corporation	Treatment of Cushing's disease.
4	Epidiolex	cannabidiol	GW Research Ltd.	Treatment of Lennox Gastaut syndrome
5	Avastin	Bevacizumab	Genentech	Treatment of patients with ovarian cancer
6	Darzalex	Daratumumab	Janssen Biotech	Treatment of multiple myeloma
7	Rubraca	Rucaparib	Clovis Oncology	Treatment of ovarian cancer
8	Blincyto	Blinatumomab	Amgen	Treatment of acute lymphocytic leukemia
9	Epidiolex	Osimertinib	Seattle Genetics, Inc	Treatment of epidermal growth factor receptor mutation-positive non small cell lung cancer.
10	Tagrisso	Blinatumomab	GW Research Ltd.	Treatment of Dravet syndrome

10	Trisenox	Arsenic trioxide	Teva Branded Pharmaceutical Products R&D	Treatment of acute promyelocytic leukemia
11	Tasigna	Nilotinib	Novartis Pharmaceutical Corporation	Treatment of chronic myelogenous leukemia
12	Crysvita	Burosumab	twza Ultragenyx Pharmaceutical, Inc.	Treatment of X-linked hypophosphatemia (formerly known as vitamin D-resistant rickets)
13	Blincyto	Blinatumomab	Amgen, Inc.	Treatment of acute lymphocytic leukemia
14	Adcetris	Brentuximab vedotin	Seattle Genetics, Inc	Treatment of Hodgkin's lymphoma
15	Tagrisso	Osimertinib	AstraZeneca Pharmaceuticals LP	Treatment of epidermal growth factor receptor mutation-positive non small cell lung cancer.
16	Epidiolex	Cannabidiol	GW Research Ltd.	Treatment of Dravet syndrome

Classification of Rare Diseases

Rare disease categorization entails grouping these conditions according to many standards, including their genetic roots, symptoms, impacted bodily systems, and therapy accessibility. Generally speaking, rare diseases are ailments that only impact a small portion of the population. In Europe, the threshold is less than 1 in 2,000, whereas in the US, a disease is deemed rare if it affects fewer than 200,000 persons. This is a thorough explanation of how uncommon diseases are categorized[15,17].

1. Classification by Etiology (Cause or Origin)

Rare diseases can be categorized according to their underlying causes, which often influence treatment strategies and prognoses. The primary classifications include:

Genetic (Inherited) Disorders: These conditions arise from abnormalities in genetic material, which may be inherited from one or both parents or may result from mutations that occur during an individual's life. They can be further divided into:

Monogenic Disorders: Resulting from mutations in a single gene, examples include cystic fibrosis and sickle cell anemia.

Multifactorial Disorders: These involve the interplay of multiple genes and environmental influences, such as cleft lip/palate or certain cases of hypertension.

Chromosomal Disorders: These are caused by structural or numerical abnormalities in chromosomes, with Down syndrome and Turner syndrome being notable examples.

Acquired Disorders: These conditions are not inherited but develop due to factors such as infections, environmental exposures, or autoimmune responses. Certain rare cancers and chronic fatigue syndrome are examples of acquired diseases.

Idiopathic Disorders: In some instances, the cause of a rare disease remains unidentified, leading to the classification of these conditions as idiopathic. Despite ongoing research, the origins of these diseases continue to elude understanding[16].

2. Classification by Clinical Symptoms or Affected Organ/System

Rare diseases can also be categorized according to the specific organ system or body part they impact. This classification is particularly beneficial for grouping diseases that exhibit similar symptoms or target particular organs:

Neurological Disorders: These rare conditions affect the brain, spinal cord, or peripheral nerves. Examples include uncommon types of epilepsy, neurodegenerative disorders such as amyotrophic lateral sclerosis (ALS), and Rett syndrome.

Endocrine Disorders: Rare endocrine conditions influence the body's hormonal systems. Congenital adrenal hyperplasia and Addison's disease serve as examples of such disorders.

Cardiovascular Disorders: Certain rare diseases affect the heart or blood vessels, including pulmonary arterial hypertension and various forms of cardiomyopathy.

Metabolic Disorders: These conditions disrupt the body's metabolic processes, often due to enzyme deficiencies. Notable examples include phenylketonuria (PKU) and Gaucher disease.

Musculoskeletal Disorders: These affect the bones, muscles, and joints. Conditions such as osteogenesis imperfecta (brittle bone disease) and Ehlers-Danlos syndrome are classified as rare musculoskeletal disorders.

Autoimmune and Inflammatory Disorders: These diseases occur when the immune system mistakenly attacks the body’s own tissues. An example includes rare variants of systemic lupus erythematosus (SLE) [17].

3. Based on Pathophysiology (Mechanisms)

Rare diseases can be categorized according to their fundamental biological mechanisms, which describe how these conditions disrupt normal physiological processes:

Metabolic Disorders: These disorders arise from abnormalities in enzymes or metabolic pathways. Notable examples include Phenylketonuria (PKU) and Mucopolysaccharidosis.

Immunodeficiencies: These conditions stem from flaws in the immune system, resulting in a heightened vulnerability to infections. An example of this is Severe Combined Immunodeficiency (SCID).

Defects in DNA Repair or Cell Cycle Regulation: Certain rare diseases are linked to mutations that impair DNA repair processes, with Bloom syndrome and Fanconi anemia being prominent examples.

4. International Classifications

Rare diseases are categorized using international systems to enhance understanding and facilitate research. For instance:

Orphanet Classification: Orphanet serves as a European platform that offers an extensive catalog and classification of rare diseases, incorporating clinical details, epidemiological data, and genetic information.

ICD-10 and ICD-11 (International Classification of Diseases): These international classification systems encompass rare diseases, enabling healthcare professionals and researchers to recognize and monitor them effectively. The ICD-10/11 framework contributes to the global standardization of rare disease diagnoses[16,17].

Challenges in Development of Orphan Orug

Financial considerations for orphan drug development-

Despite efforts to improve access, the majority of orphan drugs remain prohibitively expensive in China. With a 5% co-payment requirement, only three generic orphan drugs are deemed affordable for middle-income patients in the country. There are over 100 commercial health insurance providers available for those who can afford supplementary policies alongside government insurance. However, the coverage for chronic rare diseases is limited, encompassing only about 10 to 15 conditions[8].

One plan offered by Taikang Life Insurance Co., Ltd. provides a maximum coverage of merely 100,000 yuan for chronic diseases. For families with children diagnosed with rare diseases, out-of-pocket expenses can exceed 40%, leading to significant financial strain. Furthermore, many international medications that have not yet received approval from the CFDA are available in the "gray market," where patients must pay cash, often making these treatments inaccessible. Although the CFDA encourages the development of orphan drugs, the sustainability of the market hinges on patients' ability to afford these treatments. Professor Longjun Gu from Shanghai JiaoTong University has proposed the establishment of a fund specifically for rare diseases, funded by contributions from national medical insurance, commercial insurance, and government charity, to help alleviate costs that exceed patients' financial capabilities[7].

1. **Scientific and technical considerations in research and clinical trials-**

A significant obstacle in the approval process for rare and ultra-rare orphan drugs lies in the design of clinical trials. Traditionally, the phases of clinical trials—phases 1, 2, and 3—are executed sequentially, with each phase completed and assessed to guide the design of the subsequent phase. However, contemporary seamless trial designs are being adopted, which incorporate statistical analyses that permit the initiation of the next phase prior to the completion of the primary phase. These innovative trial designs necessitate sufficient statistical power and can be instrumental in accelerating the time to market while also minimizing the number of patients required for enrollment, thereby reducing costs for the sponsor. Such methodologies are currently under consideration for trials involving rare diseases, which present additional challenges due to limited patient populations. For instance, a recently approved medication for hereditary orotic

aciduria, a condition affecting only 20 individuals globally, was tested in a clinical trial that involved just four patients over a span of six weeks[8].

Incentive for orphan drug in USA and Europe

USA:

Financial Advantages

Tax Incentives: The Orphan Drug Tax Credit (ODTC) allows sponsors who have received orphan drug designation to claim tax credits for expenses related to clinical trials.

User Fee Exemption: Orphan drug products are not subject to the standard new drug application fees or user fees imposed by the FDA[9].

Regulatory Advantages

The Rare Pediatric Disease Priority Review Voucher Program enables sponsors who obtain approval for a drug or biologic targeting a "rare pediatric disease" to receive a voucher. This voucher can be utilized for expedited review of a subsequent marketing application for a different product.

The drug approval process may qualify for a fast-track evaluation by the FDA. Sponsors benefit from the FDA's support and guidance in formulating a comprehensive drug development strategy.

Clinical Development Advantages

The Orphan Product Grant program offers financial support for the clinical testing of new therapies aimed at treating and/or diagnosing rare diseases, thereby reducing the overall cost of drug development[9].

Marketing Advantages

Market Exclusivity: A drug that receives FDA approval for a specific indication is granted seven years of marketing exclusivity. In contrast, the exclusivity period for a new chemical entity is generally five years. For orphan drugs, the FDA will not permit the approval of a generic version for the rare disease for seven years following the initial approval. This incentive is more advantageous than conventional intellectual property patent protection and serves as a significant motivator.

Access Prior to Market Approval: Patients may have access to the orphan drug before it receives full market approval. A Treatment Investigational New Drug (t-IND) can be obtained under certain conditions, particularly in cases of compassionate use, such as:

The drug is intended for treating a serious or life-threatening condition. No alternative treatment options are available[10].

Europe

Financial Advantages Research & Development: When developing orphan medicines, companies can take advantage of various incentives, including:

Scientific guidance on study protocols, Reductions in various fees[9, 10].

Small Enterprises: The Agency encourages businesses involved in the development of orphan medicines to determine if they qualify as micro, small, or medium-sized enterprises (SMEs). These companies can access additional incentives, such as administrative and procedural support from the Agency's SME office, along with fee reductions.

Firms applying for orphan medicine designation can benefit from lower fees for regulatory activities, which include:

Assistance with study protocols, Applications for marketing authorization, Pre-authorization inspections, Requests for modifications to marketing authorizations post-approval, and

Grants: While the Agency does not provide research grants for sponsors of orphan medicines, funding may be available fromthe European Commission and other sources [11].

Regulatory Advantages

Pediatric Medicines: Medicines authorized throughout the EU that include results from a pediatric investigation plan in their product information are eligible for an extension of their supplementary protection certificate. For designated orphan medicines, this incentive grants an additional two years of market exclusivity.

Centralized Authorization Process: All orphan-designated medicines undergo a centralized assessment for marketing authorization within the European Union. This enables companies to submit a single application to the European Medicines Agency, resulting in one opinion and one decision from the European Commission, applicable

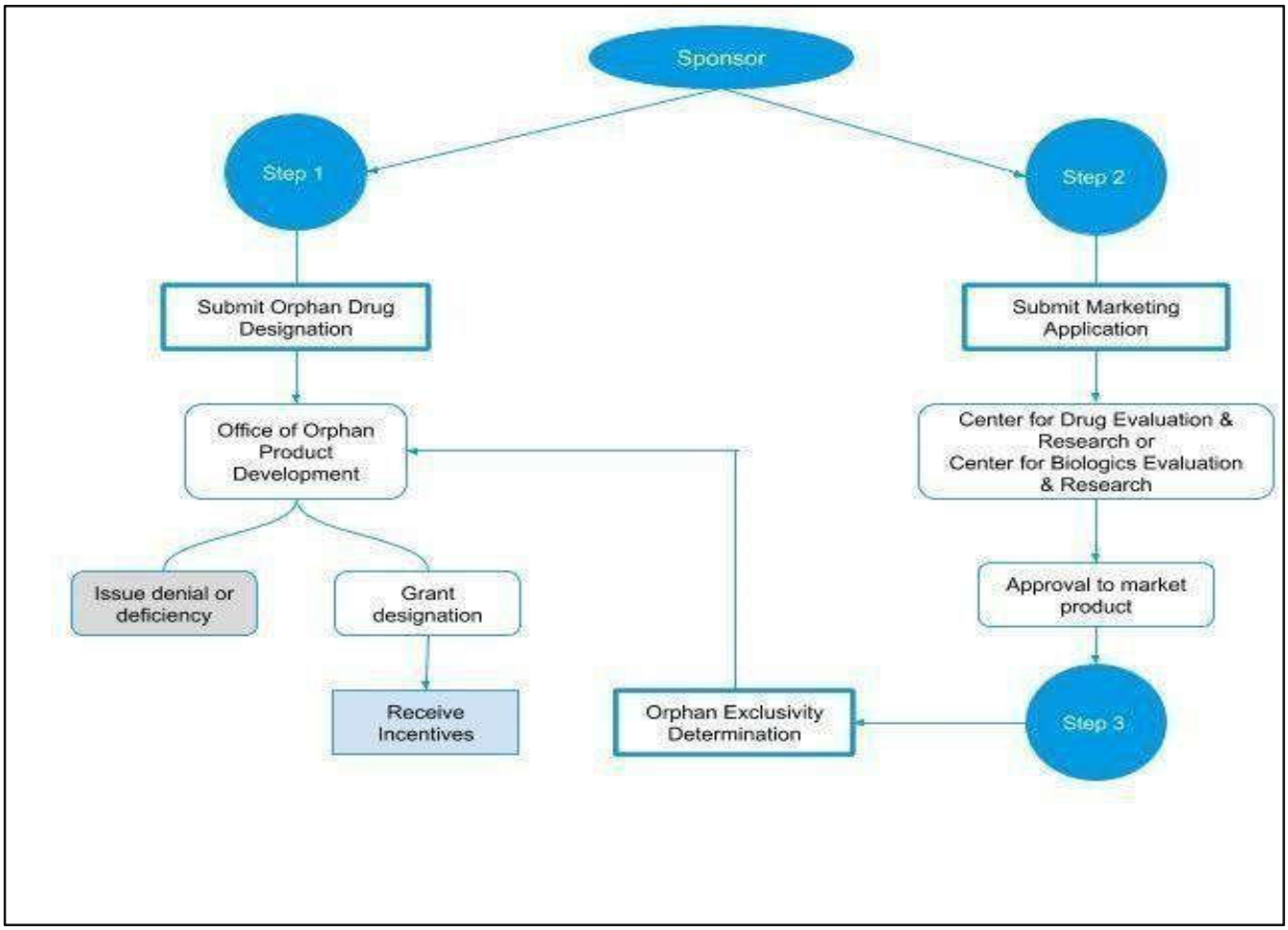
across all EU Member States. Additionally, sponsors may gain access to conditional approval through orphan designation under this centralized process[10, 11].

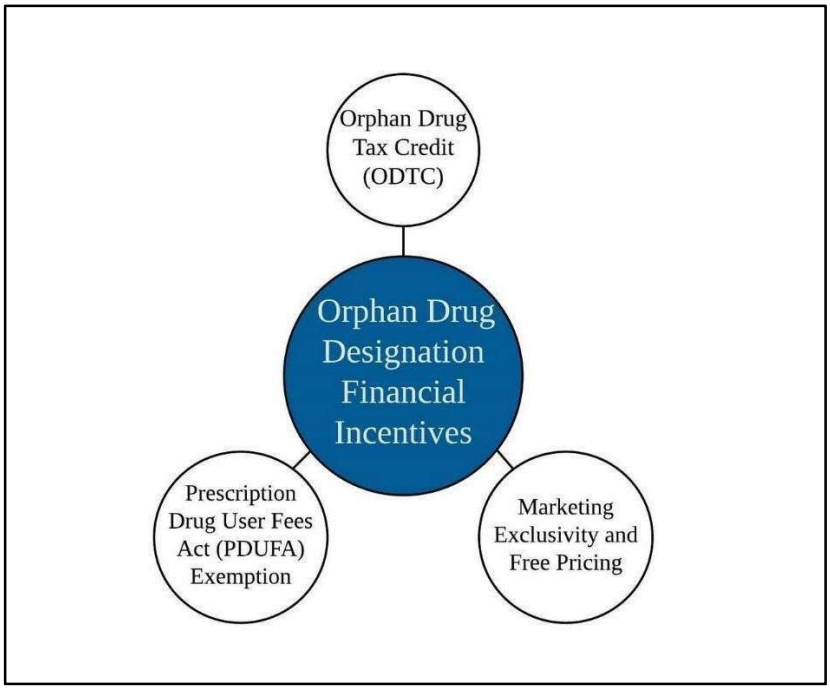
Global Benefits: The European Medicines Agency (EMA) and the Food and Drug Administration (FDA) have established joint procedures for applying for orphan designation and for submitting annual reports on the progress of designated orphan medicines[9].

Comparison of US and EU Regulatory Incentive [10]

Criteria	USA	Europe
Legal framework Regulation	Orphan Drug Act (1983)	Committee for Orphan Medicinal Products (COMP)
Administrative authorities involved	Office of Orphan Product Development (OOPD)	Committee of Orphan Medicinal Products (COMP)
Prevalence of the disease (per 10,000 individuals), justifying the orphan status	7.5	5
Marketing exclusivity	7 Years	10 Years
Tax credit or benefit	50% for clinical studies	Managed by the member states
Grants for research	programs of NH and others	FP6′ + national measures
Reconsideration of applications for orphan designation	No	Every year
Technical assistance for the elaboration of the application file	Yes	Yes
Accelerated marketing procedure	Yes	Yes – Centralized procedure

Regulatory Approval Process for Orphan Drug [1]





Current Situation and Need of Orphan Drug Regulation in INDIA

The growig awareness of orphan diseases and related medications has unfortunately not penetrated the collective consciousness of individuals in developing nations. This widespread lack of knowledge within the Indian medical community exemplifies a concerning indifference towards orphan diseases. Moreover, this ignorance cannot be explained by a scarcity of affected individuals. Estimates suggest that, as the second most populous country globally, India is home to approximately 70 million cases of orphan diseases.

The inability to grasp the epidemiological significance of these conditions in India can be linked to the absence of a comprehensive registry for orphan disease cases. In this context, the initiatives led by non-profit organizations, such as ORDI, are highly commendable. Their efforts have allowed for an "unofficial" classification of orphan diseases as those affecting 1 in 5,000 individuals or fewer within the Indian population. In addition to ORDI, numerous other NGOs are dedicated to specific disease areas, including the Foundation for Research on Rare Diseases and Disorders, the Alzheimer’s and Related Disorders Society of India, and the Down Syndrome Federation of India, among others[12].

However, the lack of governmental support or endorsement from relevant authorities raises significant concerns regarding the sustainability and effectiveness of these NGOs' initiatives. Each day, millions of Indians endure the challenges posed by orphan diseases, largely due to the absence of regulatory frameworks governing these conditions. The lack of a robust regulatory structure has far-reaching consequences, the most critical of which is the inaccessibility and unaffordability of the approximately 400 orphan drugs approved by the US-FDA. The substantial population affected by orphan diseases in India presents pharmaceutical companies with a promising opportunity for expansion.

In our opinion,

1. There needs to be a lucid and a clear definition of orphan drugs, with no room for uncertainty. A separate orphan drugs act or a small addendum to the Drugs and Cosmetics Act could suffice. We should also be clear on whether the definition of orphan drugs would include those applicable for human use or it would encompass drugs intended for veterinary use and medical devices and nutritional supplements as well.

2. Special incentives should be provided for R&D of orphan drugs. It may not be limited to monetary assistance alone. It could also include technical and personnel assistance in the foof

collaborations with government laboratories and organizations as well for conducting basic research.

3. Efforts should be made to include NGOs in the process of procurement ofdrugs at reasonable rates from other countries[11].

Orphan Drugs Market Segmentation Analysis

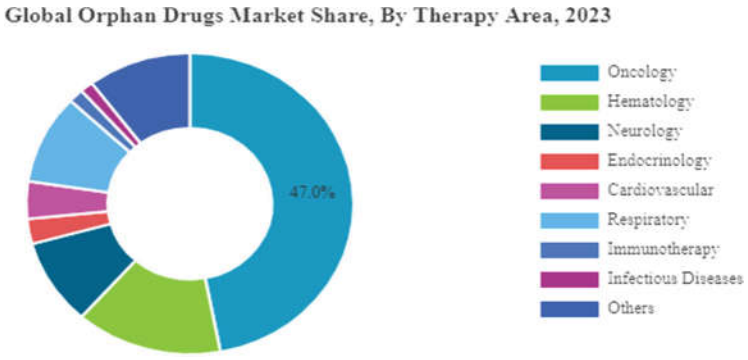
By Therapy Area Analysis

On the basis of therapy area, the market is classified into oncology, hematology, neurology, endocrinology, cardiovascular, respiratory, immunotherapy, infectious diseases, and others.

The oncology segment held a dominant orphan drugs market share in 2023. The dominance is due to the presence of several oncology drugs in the product development pipelines of key players and presence of a large number of orphan drugs dedicated to the treatment of various cancers. For instance, in February 2022, CTI BioPharma received the U.S. FDA approval for its drug Pacritinib for the treatment of adult patients with myelofibrosis, a rare bone cancer affecting over 21,000 patients in the U.S.

The hematology segment is projected to be the second most dominant segment owing to a number of new product launches and increasing number of regulatory approvals. The neurology segment is also anticipated to register a comparatively strong CAGR due to positive developments in the product offerings for chronic diseases, such as multiple sclerosis.

However, the endocrinology, respiratory, and cardiovascular segments are anticipated to register lower CAGRs during the forecast period. The immunotherapy segment is expected to register a strong CAGR due to the presence of reliable products, such as Key truda, and also increased research initiatives[14].



Clinical Trials of Orphan Drugs

Similar to all pharmaceuticals, orphan drugs are subjected to extensive testing across multiple phases of clinical trials to assess their safety, effectiveness, and suitable dosage. The phases include:

Preclinical Research

Prior to the initiation of clinical trials, preclinical research encompasses laboratory experiments and animal studies aimed at evaluating the safety and biological activity of the drug. This stage is crucial for collecting preliminary data on the drug's mechanism of action and its potential therapeutic benefits for the disease.

Phase 1 (Safety and Dosage)

Objective: To evaluate the safety profile of the drug, determine an appropriate dosage range, and recognize any potential side effects.

Participants: A limited group of healthy volunteers or patients suffering from the disease, particularly if the condition is too severe to include healthy individuals.

Duration: Generally spans several months.

Key Focus: Detect any immediate toxicities or adverse reactions associated with varying dosage levels.

Phase 2 (Efficacy and Adverse Effects)

Objective: To assess the drug's effectiveness in patients and conduct a more thorough evaluation of its safety profile.

Participants: A larger cohort of patients, typically ranging from 50 to 300, who are affected by the rare disease.

Duration: Generally spans several months to a year.

Key Focus: To ascertain whether the drug functions as intended, evaluate its effectiveness, and optimize the dosage for subsequent trials. If an orphan drug demonstrates potential during Phase 2, it may qualify for expedited approval processes.

Phase 3 (Confirmatory Efficacy and Adverse Effects Monitoring)

Objective: To validate the drug's effectiveness and safety in a broader population and to compare it against existing treatments or a placebo if no effective treatment is available.

Participants: Ranging from hundreds to thousands of patients, contingent on the prevalence of the disease.

Duration: Typically lasts a year or longer.

Key Focus: To reinforce the evidence of the drug's therapeutic advantages, along with its long-term safety and efficacy. This phase may present additional challenges for orphan drugs, as recruiting a sufficient number of participants to adequately power the trial can be difficult.

Phase 4 (Post-Marketing Surveillance)

Objective: To assess the long-term effects of the drug, including any uncommon side effects that may not have been identified in previous trials.

Participants: The broader patient population that utilizes the drug following its market approval.

Duration: Continuous for the entire period the drug remains available for sale.

Key Focus: Analyze long-term safety and efficacy[18,19, 20].

Clinical trial characteristics	Orphan drugs	Non-orphan drugs
Sample size	Small (n=96)	Large (n=290)
Randomization	Less likely (30%)	More common (80%)
Double blind	Less common (4%)	Common (33%)
Primary endpoint	Measure disease response	Measure disease progression
Comparator	None in 70% trials	Present in 80% trials
Serious adverse events	Higher (48%)	Lesser (36%)
Median duration clinical trial	Shorter (5 years)	Longer (6.9 years)
Post marketing efficacy assessment	Done in 60% cases	Done in 92% cases

Fig;3. Clinical trials of Orphan drug and Non Orphan Drug.

Post-Marketing Surveillance of Orphan Drugs

The procedures and actions that follow a drug's approval and public release are referred to as post-marketing surveillance (PMS). This stage is crucial because it enables regulators to keep an eye on the long-term effects, safety, and effectiveness of medications—particularly orphan pharmaceuticals, which are used to treat rare disorders. Although the clinical trials necessary for approval yield useful information, they frequently only include a limited, carefully chosen group of patients and are not always able to forecast how the medication will act in a larger, more varied population. Post-marketing monitoring fills in these gaps by consistently collecting empirical data[20].

1. **The Value of Orphan Drug Post-Marketing Surveillance**

Orphan medications are created for uncommon illnesses that only a small percentage of people have. Clinical trials for orphan pharmaceuticals might not adequately capture all possible side effects, pharmacological interactions, or long-term results because of the small patient population. Following licensure, these medications may also be used in a wider range of people (e.g., across age ranges or co-existing diseases), which may uncover new safety issues or therapeutic advantages not seen in clinical studies.

Essential Elements of Post-Marketing Surveillance

Post-marketing surveillance comprises various components and tools, each fulfilling distinct roles:

A. Adverse Event Reporting

Spontaneous Reporting Systems: After a drug is approved for market use, healthcare professionals and patients are urged to report any adverse events (AEs) or side effects to regulatory authorities. In the United States, this process is facilitated through the FDA Adverse Event Reporting System (FAERS), while in Europe, it is overseen by the European Medicines Agency (EMA) via EudraVigilance.

Patient-Reported Outcomes: Orphan drugs, which target specific conditions, often involve small and distinct patient populations. Many rare diseases exhibit particular symptoms or manifestations that may not be entirely captured during clinical trials, making patient-reported outcomes (PROs) vital for identifying new adverse effects or therapeutic responses that may have gone unnoticed.

Healthcare Professional Reports: Physicians and healthcare providers are instrumental in reporting adverse effects, offering essential insights into the safety profiles of orphan drugs.

Small Patient Population: Orphan drugs are specifically developed for rare diseases, resulting in a limited number of patients who utilize these treatments. This scarcity restricts the volume of data available for effective monitoring, making it more challenging to identify rare side effects or assess long-term outcomes[20,21].Given that these medications are utilized for rare conditions, healthcare providers serve as key sources of information[21].

B. Registries and Databases

Disease-Specific Registries: Numerous orphan drugs are monitored through registries or databases focused on specific diseases. These registries gather extensive data on patients' experiences with particular treatments, facilitating the assessment of drug safety and efficacy in real-world scenarios.

Orphan Drug Registries: Regulatory agencies or organizations may establish or endorse registries specifically for orphan drugs. These registries are utilized to monitor the long-term outcomes of orphan drugs, particularly for diseases characterized by slow progression or latent symptoms.

Observational Studies

Post-Marketing Observational Studies: These studies aim to observe the effects of orphan drugs within the broader population. Unlike randomized controlled trials (RCTs), observational studies provide insights into the real-world impact of these medications[20].

Regulatory Supervision of Post-Marketing Surveillance

FDA Supervision: The FDA consistently oversees orphan drugs through its Risk Evaluation and Mitigation Strategies (REMS) programs, adverse event reporting systems, and various other methods. Additionally, the FDA collaborates with manufacturers to guarantee the collection of essential post-marketing data.

EMA Supervision: The European Medicines Agency (EMA) similarly monitors orphan drugs, frequently partnering with national agencies to ensure that data collection and analysis are conducted effectively throughout Europe.

Future prospective of orphan drug

1. Gene Therapy and Genetic Modification

CRISPR/Cas9 and Genetic Modification: Gene therapy presents an opportunity to rectify the genetic mutations that lead to numerous orphan diseases. Innovative technologies, including CRISPR/Cas9 and various gene-editing methods, are being examined for their capacity to directly alter patients' genomes, potentially providing lasting solutions for genetic conditions.

Illustration: In conditions such as sickle cell anemia and thalassemia, gene therapy is already demonstrating significant potential. For uncommon genetic disorders like Duchenne muscular dystrophy (DMD) and spinal muscular atrophy (SMA), research is actively underway to develop gene therapies that could serve as one-time interventions.

Genetic Modification for Lysosomal Storage Disorders: In the case of disorders such as Gaucher disease, Fabry disease, and Mucopolysaccharidoses, gene therapies may eliminate the necessity for ongoing treatments like enzyme replacement therapy (ERT) or substrate reduction therapy (SRT). Researchers are exploring the use of gene therapies to provide patients with functional versions of the absent or faulty genes[23].

2. Cell and Stem Cell Therapy

Stem Cell Transplantation: Therapies utilizing stem cells represent a promising avenue for addressing orphan diseases. This approach focuses on employing stem cells to repair damaged tissues or to substitute malfunctioning cells. For instance, in the case of metachromatic leukodystrophy (MLD), research is underway to investigate stem cell-based therapies aimed at alleviating the neurological symptoms associated with the condition.

Ex Vivo Gene Therapy: This method entails altering a patient's cells outside the body (ex vivo) before reintroducing them to rectify genetic abnormalities. This strategy is increasingly being recognized for its potential in treating specific rare diseases, such as hemophilia and uncommon immune disorders[23,24].

3. Personalized and Precision Medicine

Customized Treatments: The expanding domain of personalized medicine signifies that therapies will increasingly be customized according to the unique genetic characteristics of individual patients. This approach is particularly crucial for rare diseases, where genetic factors can vary significantly even among patients with the same condition.

Biomarkers and genetic profiling are employed to forecast which patients are most likely to respond favorably to particular treatments. This strategy minimizes unnecessary treatment

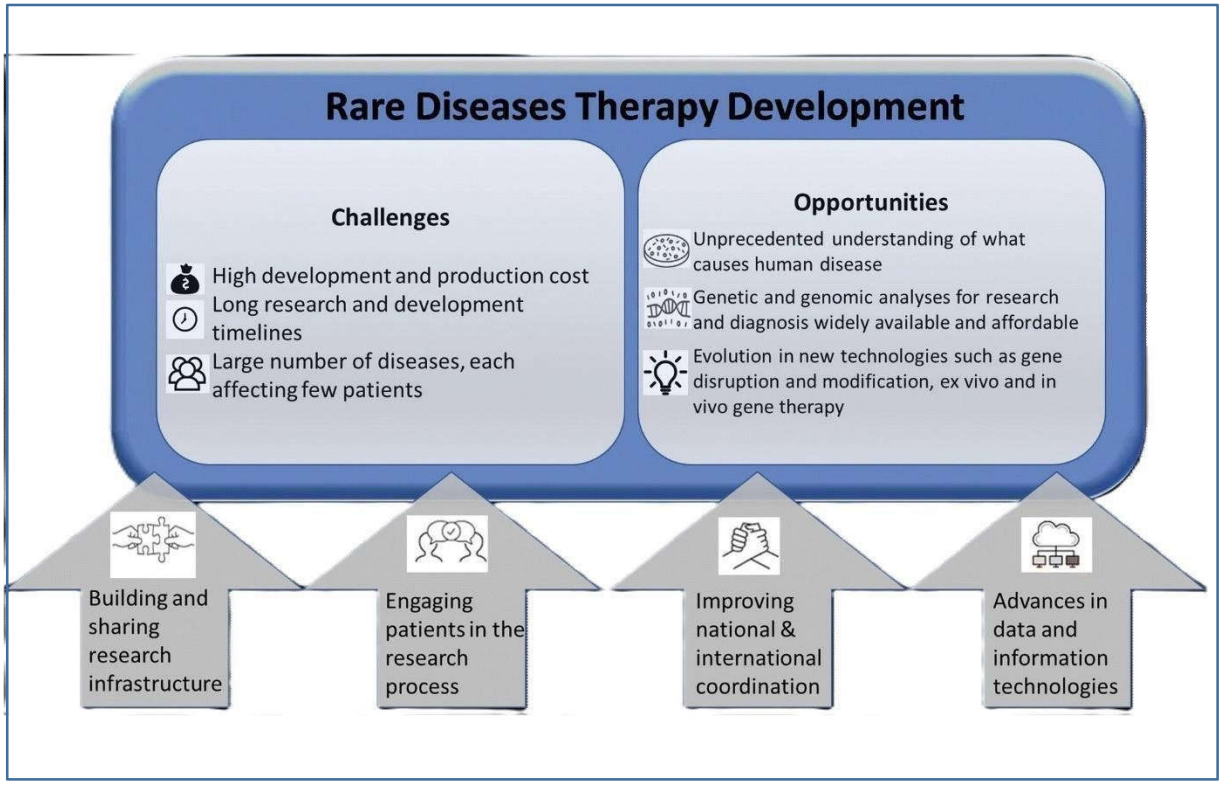
expenses and improves effectiveness by directly addressing the underlying disease mechanisms.

Companion Diagnostics: These tests are utilized to assess whether a patient is likely to benefit from a specific orphan drug. As the field of precision medicine progresses, the application of companion diagnostics will become more prevalent, allowing healthcare providers to prescribe the most suitable treatment based on the patient's genetic profile[25].

4. Advancements in Delivery Mechanisms

Enhanced Drug Delivery Systems: A significant obstacle associated with orphan drugs is the necessity for frequent or invasive administration methods, such as intravenous infusions utilized in enzyme replacement therapies (ERT). Future innovations in drug delivery systems, including nanoparticles and targeted delivery techniques, have the potential to enhance the accessibility and convenience of these treatments.

Oral Therapies: Presently, numerous orphan drugs necessitate intravenous administration, posing challenges for patients. Ongoing research is expected to yield more oral formulations of these treatments, thereby improving patient adherence and overall convenience[23,25].



Fig;4.Rare Disease Therapy Development

Case Study of Rare Disease and Orphan Drug

Gaucher Disease and the Use of Imiglucerase as an Orphan Drug

Introduction to Gaucher Disease (GD)

Gaucher disease (GD) is a rare, inherited metabolic disorder caused by a deficiency of the enzyme glucocerebrosidase (GCase), which is responsible for breaking down a lipid molecule called glucocerebroside. When GCase is deficient or absent, glucocerebroside accumulates in certain cells, primarily macrophages (a type of immune cell), leading to the formation of Gaucher cells—cells that are engorged with the accumulated substance. These cells then deposit in organs like the liver, spleen, bone marrow, and occasionally the brain.

There are three main types of Gaucher disease:

1. **Type 1 (Non-neuronopathic)** – This is the most common form and affects the liver, spleen, bones, and blood, but does not affect the brain.
2. **Type 2 (Acute neuronopathic)** – This type affects the central nervous system (CNS) and leads to rapid neurodegeneration, typically resulting in death before the age of 2-3.
3. **Type 3 (Chronic neuronopathic)** – This form also affects the CNS but progresses more slowly than Type 2[26,27].

Symptoms and Clinical Manifestations

The symptoms vary widely depending on the type of Gaucher disease, but common clinical manifestations include:

Hepatomegaly (enlarged liver)

Splenomegaly (enlarged spleen)

Bone pain and **bone fractures**, due to deposition in the bone marrow

Anemia, **fatigue**, and **easy bruising** due to blood cell involvement

Neurological issues in types 2 and 3, such as seizures, movement disorders, and developmental delays[26].

Diagnosis

Gaucher disease is often suspected based on the patient's clinical presentation (e.g., splenomegaly, bone pain) and family history. Confirmatory diagnosis involves:

Enzyme assay to measure glucocerebrosidase activity in blood or tissue samples.

Genetic testing to identify mutations in the **GBA gene**, which encodes the glucocerebrosidase enzyme.

Imaging studies, such as MRI or CT scans, to assess organ enlargement or bone damage.

Treatment with Orphan Drugs: Imiglucerase

Due to the rarity of Gaucher disease and its significant clinical burden, it is classified as an **orphan disease**, qualifying it for treatment development under orphan drug regulations. The U.S. FDA defines orphan drugs as medications developed to treat rare conditions affecting fewer than 200,000 people in the United States.

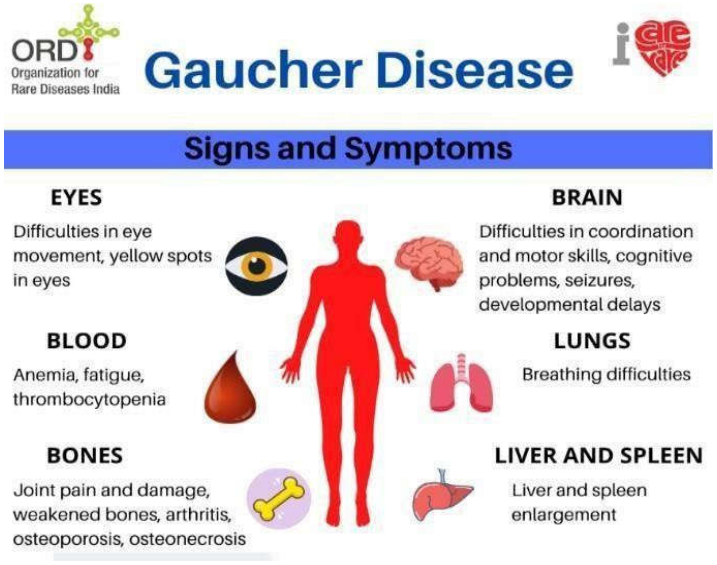
One of the most commonly used orphan drugs for treating Gaucher disease is **Imiglucerase (Cerezyme)**.[28]

Imiglucerase Overview:

Mechanism of Action: Imiglucerase is a recombinant form of the human enzyme **glucocerebrosidase**. It works by replacing the deficient enzyme in individuals with Gaucher disease. This helps break down the accumulated glucocerebroside and reduces the burden of Gaucher cells in organs like the liver, spleen, and bone marrow.

Indications: Imiglucerase is primarily used for **Type 1 Gaucher disease**, which is the most common form. It is typically administered via **intravenous infusion** every two weeks, although the frequency can be adjusted based on the patient's response.

Administration and Dosage: The dosage is based on the patient's body weight and can range from 2.5 to 60 units per kilogram of body weight. Dosage adjustments are made depending on the patient's clinical response, including improvements in liver and spleen size and marrow function[29].



Fig;5.Gauchers Disease

Top 10 Pharma Companies Manufacturing Orphan Drug

Sr. No	Pharma company	Approved drug	Indication
1	Pfizer	VYNDAQEL (tafamidis meglumine)	transthyretin amyloid cardiomyopathy (ATTR-CM)
2	abbvie	Veliparib	non-small cell lung cancer.
3	Novartis	Fabhalta (iptacopan)	paroxysmal nocturnal hemoglobinuria
4	Amryt	FILSUVEZ® (Oleogel-S10)	Epidermolysis Bullosa (EB)
5	Amgen	Tepezza (teprotumab)	thyroid eye disease (TED).
6	Gsk pharm.	Elraglusib	soft tissue sarcoma (STS).
7	Johnson Johnson	Darzalex	multiple myeloma
8	Sanofi	Xenpozyme	Niemann-Pick disease
9	Roche	Esbriet (pirfenidone)	Idiopathic Pulmonary Fibrosis (IPF).
10	Takeda	EXKIVITY	non-small cell lung cancer

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