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Usa Orphan Drug Legislation and Incentives for Orphan Drug Development

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Rare Diseases

The terms rare disease and Orphan Disease are often used interchangeably. In USA any disease that effects less than 200,000 people is termed as a rare disease. Rare diseases are often misdiagnosed due to lack of adequate history and patient population. These diseases generated little interest with pharmaceutical companies, researchers, and clinical experts historically due to uncertainty of cost recovery as treated population is low. As a result, research, and development activities as well as investments on these drugs were less. Lack of *financial incentive, high cost of development and unclear roadmap of cost recovery resulted in rare disease drugs being neglected* from both development and marketing perspective.

National Institutes of Health (NIH) has estimated that between 25–30 million citizens in the United States of America (USA) are suffering from at least one out of around 7000 rare diseases. It has been found that there was no clear health policy and experts in these fields were very less. These two factors caused late diagnosis and poor access to proper healthcare for people suffering from these diseases. Only a few experts caused misdiagnosis and unwillingness of patients to get treated due to associated costs caused fragmented information around the natural history of rare diseases.

Defining and counting rare diseases is not straightforward. Difficulties in obtaining definitive diagnoses contribute, as do limitations in systems for reporting and tracking such diagnoses. Therefore, the epidemiology of rare diseases—including the determination of prevalence (the number of people affected at any one time), incidence (the number of new cases each year), and patterns of disease (e.g., age distribution) in the population—is inexact. Below are few examples of rare diseases in USA as per therapeutic class.

Table 1: Examples of Rare diseases based on therapeutic class

Therapeutic Class	Disease/Disorder
Haematology	• Sickle Cell Disease • Myelofibrosis • Aplastic Anemia
Infectious diseases	• Rocky Mountain Spotted fever • Lemierre's syndrome • Mucormycosis
Neurology	• Parkinson's disease • Neuronal Ceroid Lipofuscinosis • Amyotrophic Lateral Sclerosis
Metabolic	• Fabry's disease • Mucopolysaccharidosis • Gaucher disease
Oncology	• Leiomyosarcoma • Infantile Myofibromatosis • Inflammatory Myofibroblastic Tumor

Causes of rare disease

Some rare conditions have multiple types of causes. Below are listed the probable factors resulting in a rare disorder:

a. **Genetic causes**: Great majority of rare diseases (~80%) are genetic in origin (see, e.g., NORD, 2007; NIH, 2008). Many are caused by defects in a single gene, for example, alpha1-antitrypsin deficiency (which may cause serious lung or liver disease) and Friedreich's ataxia (a neurological disorder that may also be accompanied by cardiac and other problems). In some rare conditions, multiple genes may contribute collectively to

manifestations of the disorder (Dale and Link, 2009). Rare genetic conditions are often inherited but may also arise as a result of sporadic or chance mutations.

b. **Infectious agents**: Several rare diseases have infectious causes. Some infections (e.g., those caused by Balamuthia mandrillaris and Chromobacterium violaceum) are thought to be rare worldwide (de Siqueira et al., 2005; Glaser et al., 2008). Research suggests that genetic factors may affect susceptibility to infectious agents, either increasing susceptibility or having a protective effect.

c. **Toxic Agents**: Some rare diseases or conditions result from exposure to natural or manufactured toxic substances, including substances that appear as product contaminants. In the United States, examples include arsenic and mercury poisoning, mesothelioma (a cancer caused by exposure to asbestos), and eosinophilia-myalgia syndrome, which is associated with contaminated (or overused) tryptophan, a dietary supplement.

d. **Other Causes**: Rare conditions may have a variety of other causes. Examples include conditions caused by nutritional deficiencies (e.g., beriberi, which results from thiamine deficiency and is rare in the United States [Medline Plus, 2008]) and injuries (e.g., commotio cordis, in which ventricular fibrillation and sudden death is associated with a nonpenetrating blow to the chest [Maron and Estes, 2010]). Certain rare conditions are caused by the persistent adverse or toxic effects of treatment for another disease. For example, the Office of Rare Diseases Research, NIH (ORDR) list of rare diseases includes radiation-induced meningioma, which is a rare central nervous system tumour.

Prevention, Diagnosis, and Treatment

Prevention:

a. *Primary Prevention*: Primary prevention seeks to eliminate or reduce risk factors that cause disease. Prevention is a mainstay of the infection control programs of public health agencies. Common primary prevention measures include immunizations (which are usually aimed at conditions that are or have been relatively common) and hand washing and other basic sanitation measures that are employed to control both common and rare infections. Preventive measures for certain rare diseases like few serious genetic conditions, such as thalassemia involve very personal and intimate decisions about marriage and childbearing High-risk couples may be advised about a range of options, including avoiding marriage to another person who is a carrier for the same disease, using contraceptive methods to avoid pregnancy, undergoing in vitro fertilization with embryonic screening, or obtaining prenatal screening with the possibility of pregnancy termination or planning for the birth of an affected child.

b. *Secondary Prevention*: Secondary prevention strategies involve screening or testing to identify a condition so that effective treatments can be provided to people before the onset of debilitating symptoms or complications. Newborn screening programs, which use biochemical or genetic blood tests, are prominent examples. In 2005, the American College of Medical Genetics (ACMG) recommended screening for 29 mostly inherited, serious, rare conditions (Watson et al., 2006). These recommendations were endorsed by a U.S. Department of Health and Human Services advisory panel on heritable disorders and genetic diseases in infants and children (Howell, 2005). As described by the ACMG, the conditions fall in five broad categories: organic acid metabolism disorders, fatty acid oxidation disorders, amino acid metabolism disorders, hemoglobinopathies, and other disorders.

Diagnosis

The diagnosis of many rare diseases has been limited historically by imprecise, cumbersome, or expensive testing and by limitations on physician and patient access to the most up-to-date information about rare diseases (including diagnostic criteria) and other diagnostic resources. Clinical specialization and sub specialization also contribute to the extent that specialists focus on their piece of a patient's complex of symptoms. For example, because of multiorgan involvement, patients with cystic fibrosis may be diagnosed by pulmonologists, gastroenterologists, allergists, or general paediatricians.

Treatment

The below table illustrates the range of treatments—from surgery to diet and from stem cell therapy to environmental adaptation—that may be deployed for specific rare conditions.

Table 2: Examples of treatment for rare conditions

Source: Committee on Accelerating Rare Diseases Research and Orphan Product Development. Rare Diseases and Orphan Products: Accelerating Research and Development. Field MJ, Boat TF, editors. Washington (DC): National Academies Press (US); 2010.

Therapeutic Category	Treatment Example	Rare Condition
Small-molecule compounds	Imatinib	Chronic myelogenous leukemia
Protein therapies	Enzyme replacement therapy	Gaucher disease
Metabolic therapies	Sodium phenylbutyrate	Urea cycle disorders
Nutritional therapies	Phenylalanine-restricted diet	Phenylketonuria
Environmental modification or adaptation	Avoidance of sunlight	Xeroderma pigmentosa
Stem cell transplants (investigational)	Neural stem cell transplant	Neuronal ceroid lipofuscinosis
Genetic therapies (investigational)	Exon skipping	Duchenne muscular dystrophy

Treatments may be of three types:

- *Curative*: Truly curative treatments for rare conditions are themselves rare. Immediate treatment may be completely successful for all or most cases of certain rare infections (e.g., Tropheryma whipplei) or certain rare poisonings (e.g., from snakebites or cyanide)
- *Disease modifying*: Disease-modifying therapies are targeted to the underlying pathology of a disease in order to prevent its progression or otherwise limit the harm it creates. For many disease-modifying therapies, the treatment effect is short-lived and must be repeated indefinitely. Examples include enzyme replacement therapies for conditions such as Gaucher disease
- *Symptom or function modifying*: Symptomatic treatments are vital to patient well-being for many chronic rare conditions, especially when more definitive therapies are not available. Treatments also seek to treat or prevent other disease- or treatment-related complications, for example, infections (such as the bronchitis or pneumonia caused by cystic fibrosis or primary ciliary dyskinesia) and anaemia (such as that associated with hereditary spherocytosis)

Orphan Drugs

The Orphan Drug Act of 1983 defines an orphan drug as in general, medicines (including biological products) intended for people with rare diseases, that is, diseases affecting fewer than 200,000 people in the United States. If, however, the drug is a vaccine, diagnostic drug, or preventive drug, then orphan designation is possible if the drug would be administered in the United States to fewer than 200,000 per year.

Moreover, if it is to treat a disease that affects a larger number of people, then a drug may be still designated as an orphan in certain situations in which there is no reasonable expectation that costs of research and development of the drug for a particular medical indication can be recovered by sales in the United States.

Drugs, including orphan drugs, are designated, and approved for specific indications. An indication describes a particular use of a drug or device. Few examples of orphan drugs approved for usage in USA is given below:

Table 3: Examples of orphan drugs

Source: Miller, K.L., Fermaglich, L.J. & Maynard, J: Orphanet J Rare Dis. 2021; 16: 265

Generic Name	Therapeutic Area	Broad Category	Product Type
Diaziquone	Oncology	Oncology	Drug
Alpha-1-Antitrypsin (Recombinant DNA Origin)	Pulmonary	Pediatric-Onset	Biologic
Altretamine	Oncology	Oncology	Drug
Pentamidine Isethionate	Infectious Diseases	Infectious Diseases	Drug
Levocarnitine	Metabolism	Pediatric-Onset	Drug
Cromolyn Sodium	Hematology	Pediatric-Onset	Drug
Bacitracin	Infectious Diseases	Infectious Diseases	Drug
Hemin	Metabolism	Adult-Onset	Biologic
Ethanolamine Oleate	Gastroenterology	Adult-Onset	Drug
Botulinum Toxin Type A	Ophthalmology	Pediatric-Onset	Biologic

USA Orphan Drug Legislation

In 1983, *Orphan Drug Act* was introduced in USA which has managed to *bring in regulations and to provide incentives to support R&D of orphan drugs*. Patient organizations have been formed to support these programs and various grants and incentives are given by the agencies to sponsors and researchers to work more on rare therapeutics. There is significant development in the domain of orphan drug research, and many breakthrough therapies and new treatments have been developed since inception of Orphan Drug Act supported by scientific advancements as well as new technological innovations.

Incentives for Orphan Drug Development

- *Seven years' marketing exclusivity* from the date of marketing approval of a drug with an orphan designation. During this period, no other sponsor may obtain approval of the same drug for the same use except under limited circumstances, but FDA may approve a different drug for the same indication. *Exclusivity is available to patented as well as unpatentable drugs*
- *Tax credit of up to 25 percent for qualified expenses* for clinical research to support approval of an orphan drug
- *Grants to support clinical development* of products for use in rare diseases
- *Exemption (through the FDA Modernization Act of 1997) from several kinds of user fees* that are normally charged to sponsors like Prescription Drug User Fee Act (PDUFA) (passed by United States Congress in 1992 for collection of application fees for approval of new drugs)
- *Recommendations from FDA staff to sponsors about nonclinical and clinical studies* that would support approval of a drug for a rare disease. Other special assistance, such as accelerated approval or fast track or priority review may also be available for sponsors of orphan drugs

In addition to the above, there are research and development related incentives also extended to sponsors:

- Trials for Orphan Drugs can be single arm (no placebo), open label or non-randomized. *Phase 1 safety trials can be skipped, and Phase 2 and 3 trials* can be combined in case of low patient population
- Orphan drug sponsors can utilize expedited pathways of Food and Drug Administration (FDA) programs. These programs are *Fast Track Designation, Breakthrough Therapy Designation, and Priority Review* of applications, as well as the Accelerated Approval pathway of orphan drugs. The sponsors are also eligible for Orphan Products Clinical

Trials Program

- Data related to treatment experience are collected from patients, caregivers, immediate members from family and foundations supporting the specific disease through FDA facilitated *Patient Focused Drug Development meetings* (PFDD). Orphan Drug developers can determine clinical endpoints as well as therapy administration route for clinical trials based on the patient data

Role of Office of Orphan Products Development

The Orphan Drug Act empowered the FDA to review and approve requests for orphan drug status, coordinate drug development, and award research grants. The FDA created the *Office of Orphan Product Development (OOPD)* to help manage this regulatory function. Although the initial legislation permitted manufacturers to apply for orphan product designation at any time, a 1988 amendment required sponsors to apply for orphan designation before submitting applications for marketing approval.

The FDA Office of Orphan Products Development (OOPD) supports and advances the development and evaluation of new treatments for rare diseases. OOPD evaluates information from product sponsors to determine if drugs, biologics or medical devices meet the criteria for certain incentives and administers grants to provide funding for research on rare diseases. The office also works on rare disease issues with medical and research communities, professional organizations, academia, government agencies, industry, and rare disease patient groups.

Responsibilities of OOPD are:

- Work with sponsors to determine if their products meet the criteria for certain categories (e.g., orphan drug, rare pediatric disease drug or humanitarian use device designations)
- *Provide orphan status to drugs and biologics* which are intended to treat, diagnose, or prevent rare diseases that affect fewer than *200,000 people in the U.S*
- *Designate medical devices* that intend to *benefit patients in treating or diagnosing a disease* or condition that affects fewer than *8,000 individuals in the U.S. per year*
- Work with the *Office of Pediatric Therapeutics* and product centers to determine rare pediatric disease designation for drugs or biologics that meet certain criteria.
- Award grants to provide funding for clinical trials and natural history studies that advance rare disease medical product development
- Award grants that provide funding to develop nonprofit consortia to facilitate pediatric medical device development

Role of Centre for Drug Evaluation and Research (CDER)

CDER is responsible for reviewing and approving New Drug Applications for orphan drugs along with regular therapeutics. Large part of orphan therapeutic approvals is taken care of by CDER. In general, the review divisions of CDER are organized around rare disease therapeutic areas.

FDA created a position within CDER, the Associate Director for Rare Diseases, who serves as the centre's lead person on issues involving orphan drugs and rare diseases. The office taking care of the same is *Office of Rare Diseases, Paediatrics, Urologic and Reproductive Medicine-Division of Rare Diseases and Medical Genetics* (DRDMG). Responsibilities of the Associate Director includes:

- Serving as the primary contact for the rare disease community
- Assisting developers of drug and biologic products in understanding and following relevant regulatory requirements
- Coordinating the development of policies within CDER for the review and approval of drugs for rare conditions
- Encouraging collaboration among CDER scientists and clinicians

The *Division of Rare Diseases and Medical Genetics* (DRDMG) serves as a hub for rare disease drug development across the Office of New Drugs by coordinating rare disease education, policy, research and stakeholder engagement. DRDMG also regulates

Investigational New Drug Applications (INDs), New Drug Applications (NDAs), and Biologics License Applications (BLAs) for drugs and biologics intended for the prevention and treatment of rare inborn diseases.

Key highlights of OOPD designations

- At any stage between preclinical phase up to marketing approval submission, request for orphan designation can be submitted
- Orphan Drug Modernization Plan in 2017 ensured streamlining of the designation review process and fixing the review timeline to 90 days. This resulted in increase in proportion of designations
- There was 1500% increase in oncology designations (from 73 in 1980s to 1163 in 2010s). National Cancer Institute under the National Institutes of Health sponsored grants resulted in scientific advances in cancer research. Clinical trial grants for rare diseases including cancer are also provided by OOPD
- *Tropical Disease Priority Review Voucher* and the *Generating Antibiotic Incentives Now* (GAIN) Act passed in 2012 as part of Food and Drug Administration Safety and Innovation Act (FDASIA) contributes to orphan drug research for infectious diseases
- Approval of biologic orphan products have undergone increase over decades, but the proportion of designated biologic has remained constant
- Orphan biologic products have been found to have higher rate of success of approvals, if compared to orphan drug products. *Pathogenic specificity of a specific rare disease, sponsor expertise in biologic development and knowledge of rare disease history* has resulted in higher approval of biologic

1. FDA Programs regarding Orphan Drugs Designation and Approvals

Because orphan drugs are often developed to treat patients with unmet medical needs, they may be eligible for one or more of FDA's expedited programs. FDA's four expedited programs—accelerated approval, breakthrough therapy designation, fast track designation, and priority review—are intended to facilitate and expedite the development and review of new drugs to address unmet medical needs in the treatment of a serious disease.15 Depending on the type of expedited program, manufacturers of new drugs may receive a variety of benefits, such as additional opportunities to meet with and obtain advice from FDA officials during drug development or a shorter FDA review time goal for the marketing application. The programs are described below:

- **Fast Track**: Fast track designation process helps in expediting review and facilitating development of drugs that can be used to treat unaddressed and critical medical conditions. The designation request must be submitted by the drug development company, or the sponsor and the submission can happen any time during the process of drug development. Based on evidence supporting that the drug can be used to treat rare conditions, FDA decides on the designation within a period of sixty days. The approval is granted by "Office of the Commissioner, Fast Track"
- **Breakthrough Therapy**: Breakthrough Therapy designation helps in expediting review and facilitating development of drugs that can be used to treat a serious medical condition. Additionally, the drug should contain evidence that it is able to provide improved therapy based on significant clinical endpoints as compared to currently available treatments. The designation request should be submitted by the drug development company to FDA. The request should ideally be submitted latest by the end-of-clinical trial phase-2 meetings, for features of designation to be obtained. Within sixty days of receipt of request for designation, FDA responds to the same. The approval is granted by "Office of the Commissioner, Breakthrough"
- **Accelerated Approval**: Accelerated approval regulations of FDA is meant for drugs that can be used to treat a serious or unmet medical condition. As per the regulations, drugs are approved based on a surrogate endpoint, thus resulting in faster approval of these drugs by FDA. The approval is granted by "Office of the Commissioner, Accelerated Approval"

- **Priority Review**: FDA decides on Priority Review applications within 6 months. Every application is reviewed for grant of designations. The application is meant for drugs which can be either original or efficacy supplemental drug and will be used to treat serious medical conditions. In addition, the drug should also demonstrate ability of significantly improved safety and effectiveness as compared to existing therapies, post approval. Priority Review within 60 days of receipt of NDA, BLA or efficacy supplement application, designation outcome is provided by FDA. The approval is granted by "Office of the Commissioner, Priority Review"

2. Types of Orphan Regulatory Approval

- **Orphan NME approval:** Approval of New Molecular Entity (NME) based on clinical and pre-clinical safety and efficacy studies by FDA for a rare disease indication for the first time in USA
- **Orphan secondary indication:** newer indications related to rare disease treatment can arise for an already approved drug which is called "Secondary Indication" that includes**:**

➢ Indications for a disease that is different from the first or originally approved indication

➢ Extension of indication to different patient population, e.g., approval of a drug for pediatric use that was already approved for adults

- **Orphan new formulation:** new formulations for an already approved drug used to treat rare or non-rare disease

3. Orphan Products Grants Program

FDA has two Orphan Drugs Grants Program. These grants are provided to the researchers for developing safe and effective drugs for treatment of rare diseases. FDA also funds study of Natural History of Rare Diseases, since 2016. These studies address unmet medical needs of rare disease patients. The two grants program that are managed by Office of Orphan Products Development are:

- **Clinical Trials Grant Program**: This program provides grants for research, development and clinical trials of Orphan products that can significantly improve the safety and effectiveness of treatment of rare diseases. This grant program ensures timely development of orphan drugs without huge initial investment. At a given point of time, *FDA sponsors around 60 to 85 research projects*. FDA facilitates the drug development process by promoting innovative clinical trial designs (e.g., adaptive, basket, umbrella trials), and suggesting innovative technologies to support trials in low population. (e.g., data modelling and simulations). FDA promotes enhanced use of existing infrastructure, early and continuous engagement with patients during drug development process and increased association with stakeholders. Since 1983, the Clinical Trial Grants Program has supported research, development, clinical trials, and subsequent approval of ~70 products meant to treat rare disease conditions
- **Natural History Studies Grants Program**: Natural History Studies Grant Program was launched by OOPD in 2016. The program was implemented to bridge disease knowledge gaps, support of orphan drugs clinical trials and support advancement of rare disease research and development of orphan drugs. Since inception of the grants program in 2016, *OOPD has supported two research projects with value $13.5 million out of which $3.5 million was granted in partnership with National Centre for Advancing Translational Sciences (NCATS) under National Institutes of Health (NIH)*

4. Regulatory Framework of Orphan Drugs in USA

For drug manufacturers seeking to develop and receive FDA approval to market an orphan drug, orphan designation is a separate process from. Orphan Designation is required for a drug to be eligible to receive FDA grants for performing research and development activities and clinical trials and other incentives for drug development. Marketing review process follows the same principles and guidelines as required for other drugs, including safety and efficacy evidencing, scientific advisory etc. Below is a depiction of the *Orphan Drug*

Regulatory Framework in USA.

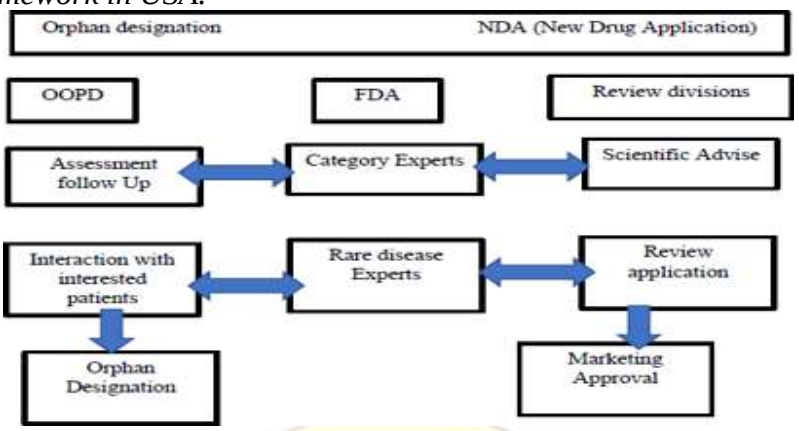

Figure 1: Drug Regulatory Framework in USA.

Source: Orphan Drugs: FDA Could Improve Designation Review Consistency; Rare Disease Drug Development Challenges Continue. (n.d.). In https://www.gao.gov/products/gao-19-83

5. Orphan Designation Eligibility and FDA's Designation granting process

FDA's Office of Orphan Products Development (OOPD) administers the orphan drug program and evaluates orphan designation applications. OOPD implemented 90-days application review timeline goal as part of Orphan Drug Modernization Plan of 2017.

➢ Eligibility for obtaining orphan designation

There are a variety of circumstances under which a manufacturer's drug is eligible for orphan designation. A drug is eligible for orphan designation when:

- A drug intended to treat a disease that *affects fewer than 200,000 people in the United States*
- A drug is also eligible *for orphan designation when it is intended to treat a disease that affects 200,000 or more people in the United States and there is no reasonable expectation of recovering the cost* of drug development and marketing from U.S. sales
- A drug that is intended to *treat a specific population known as orphan subset of a non-rare disease* is eligible for orphan designation when a property of the drug (e.g., *toxicity profile, mechanism of action, or prior clinical experience*) limits its use to *this subset of the population*

➢ Orphan Designation Process

The manufacturer can submit an orphan designation application at any point prior to submitting a marketing application. When a drug manufacturer submits a designation application, *OOPD receives and assigns it to a reviewer based on factors such as prior experience related to a particular rare disease and workload across OOPD reviewers*.

The drug manufacturer's application is required to include such items as:

- A *description of the rare disease*, documentation of the number of people affected by the disease in the United States (*the population estimate*)
- A *scientific rationale* explaining why the *drug may effectively* treat the disease
- Contains early drug development data for the drug's intended use in the rare disease.

OOPD guidance requires reviewers to perform certain tasks when making decision on an orphan designation application. Reviewers are required:

- To evaluate the *manufacturer's application*
- To *record information about the drug and disease* on a standard review template
- To independently *verify certain information* included in the application
- To verify the *population estimate provided by the manufacturer* based on independent resources, including comparing the population estimate against prior related orphan designations

Once the OOPD reviewer's decision is recorded on the standard review template, it undergoes a *secondary review by two independent reviewers* including the Director of the Orphan Drug Designation Program. This secondary review is intended:

- To ensure the *quality of the application review*
- To ensure the *consistency of the review* across all related designation applications

There are three possible outcomes from the designation review:

- The *orphan designation is granted*
- The *application is pending* with the manufacturer due to OOPD finding it deficient
- The *orphan designation is denied*

OOPD sends *the drug manufacturer a decision letter detailing the outcome of its review*. If the application is pending or denied, the decision letter describes OOPD's concerns with granting the orphan designation one of which can *insufficiently evidence to support its scientific rationale*. The manufacturer may address these concerns by:

- An amendment to the original application for applications in *pending status*
- A new application for applications in *denied status*

The flow is depicted in the below diagram:

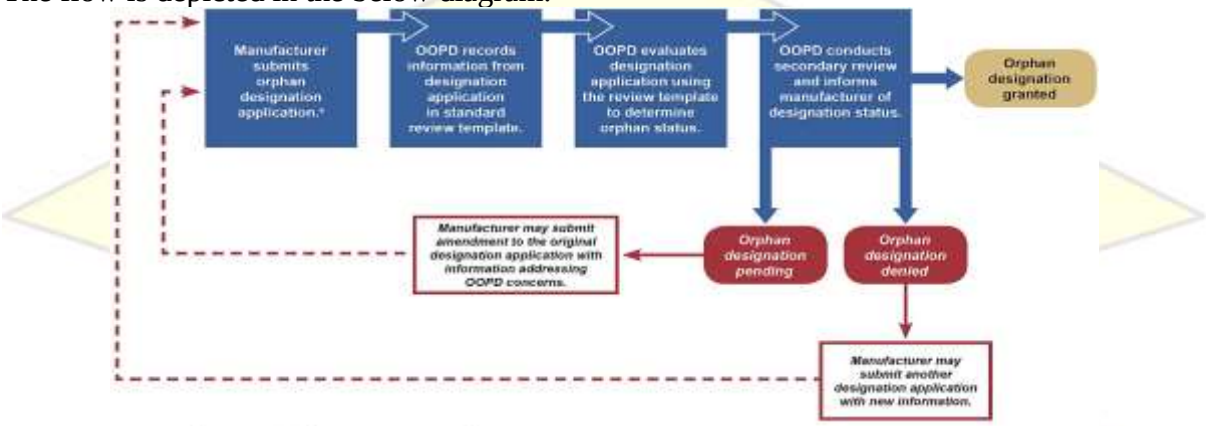

Figure 2: Office of Orphan Products Development's (OOPD) Orphan Designation Process

Source: Orphan Drugs: FDA Could Improve Designation Review Consistency; Rare Disease Drug Development Challenges Continue. (n.d.). In https://www.gao.gov/products/gao-19-83

➢ Marketing Approval Process

FDA's marketing approval process for orphan drugs follows the same process as that of other drugs. Manufacturer applies for *marketing approval to FDA post safety and efficacy assessment through preclinical testing and clinical trials*. The two FDA centres responsible for reviewing applications to market drugs in the United States are the *Centre for Biologics Evaluation and Research (CBER)* and the *Centre for Drug Evaluation and Research (CDER).* To obtain marketing approval, a drug manufacturer submits its research in a new drug application (NDA) or biologic license application (BLA) to FDA, which then reviews and approves the drug for marketing if it is shown to be safe and effective for its intended use.

Upon *completing its review of a marketing application*, FDA will send *an action letter* with its determination to the drug manufacturer. The *time elapsed from the date FDA receives the application to the date it issues an action letter* informing the drug manufacturer of the agency's decision is defined as *one review cycle*. If FDA does not approve the marketing application and the drug manufacturer resubmits the application, a new review cycle begins. When FDA approves a drug manufacturer's marketing application, it approves the *drug to treat one or more specific uses, known as indications*. The approved indication is based on the clinical trial data provided in the manufacturer's marketing application. For example, one drug was *granted orphan designation for the treatment of cystic fibrosis*, while the drug's marketing approval was for the treatment of cystic fibrosis in patients *12 years and older who have a certain genetic mutation* (the indication). Overall approval rates for all drugs are high with around *90 percent of submitted marketing applications* are ultimately approved.

The orphan drug marketing exclusivity incentive only applies to the drug's approved indication. OOPD *determines orphan drug marketing exclusivity* after receiving notification

of the drug's marketing approval from CBER and CDER. The below diagram depicts the market approval flow:

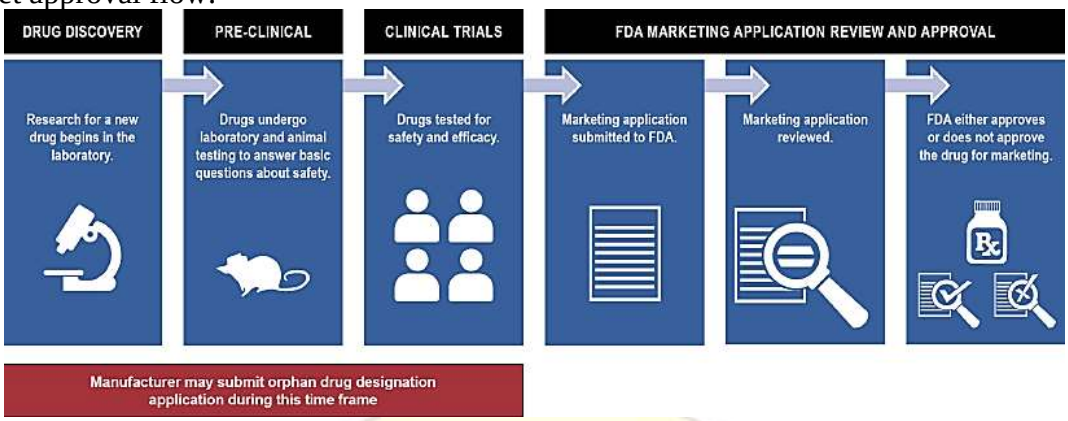

Figure 3: Drug Development and FDA Marketing Approval Process Steps.

Source: Orphan Drugs: FDA Could Improve Designation Review Consistency; Rare Disease Drug Development Challenges Continue. (n.d.). In https://www.gao.gov/products/gao-19-83

Below diagram depicts the *Orphan Drug Lifecycle in USA*.

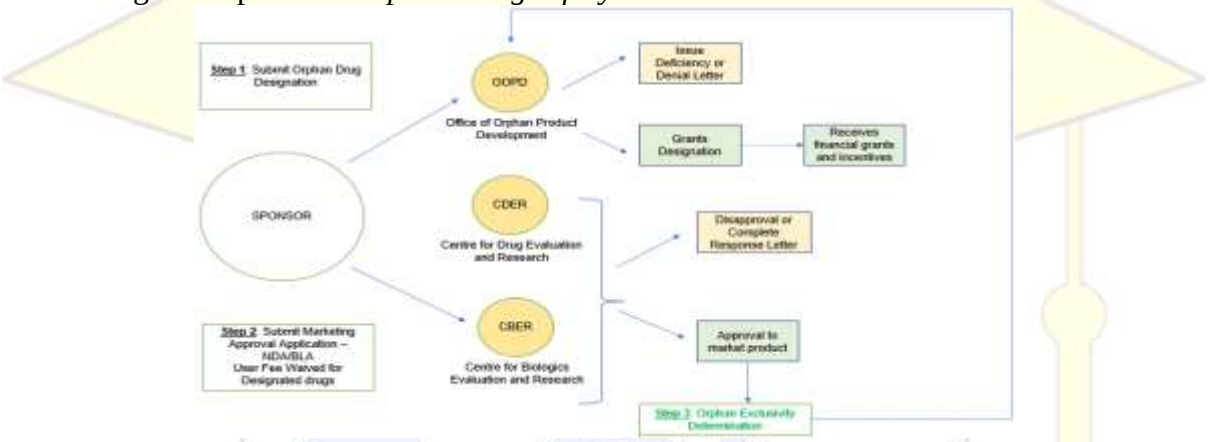

Figure 4: Orphan Drug Lifecycle in USA

Source: Orphan Drugs: FDA Could Improve Designation Review Consistency; Rare Disease Drug Development Challenges Continue. (n.d.). In https://www.gao.gov/products/gao-19-83

6. The Role of Patient Organizations

A group of patient families in the 1980s in the USA served as the inspiration for the 1983 passage of the Orphan Drug Act, which would eventually become known as the National Organization for Rare Disorders (NORD). Patient organizations today makes significant contribution towards orphan drug research which includes but not limited to creating awareness about disease among general public, performing data collection on rare disorders, providing assistance and therapeutic information to families of effected patients, promoting scientific research through granting awards and incentives, maintaining centralized registries of patients, collecting specimens in biobanks, and working together with academic institutions, business organizations, and government agencies. The largest umbrella patient organizations are NORD in the United States and European Organization for Rare Diseases (EURORDIS) in Europe. To further coordinate their efforts, these two organizations recently inked a strategic collaboration agreement. In addition to being the people best suited to understand their condition, patient representatives have also gained more authority in all facets of their disease, including knowledge collecting, financial and non-financial support for basic research, partnership in clinical research, working with regulatory agencies, taking pricing and reimbursement decisions, along with other supporting activities.

7. Challenges in orphan drug development in USA

Despite recent successes in developing orphan drugs, less than 10 percent of patients with rare diseases. While the ODA had some benefits, there are major problems that needs to be addressed:

- **High Pricing**: High cost of medication is making treatment accessibility difficult. USA follows free pricing where manufacturers can fix prices of pharmaceuticals. This causes premium pricing for orphan products. Average cost of treatment is $32,000 with few treatments have cost more than $500,000. Insurance pay-outs are not sufficient to cover the expenses of costlier drugs with 20%-33% of costs managed by patients
- **Concentration of research on Oncology**: Incentives are unable to stimulate innovation across all therapeutic areas and major innovations are still focused on cancer treatment
- **Manufacturing Hurdles**: Orphan drugs are in many cases formulated at high concentrations and administered to limited patient populations, leading to manufacture much smaller quantities. The drug substances are also often highly complex, requiring novel and sophisticated synthetic routes and production methods. The high value and limited quantity of these materials (drug substance and drug product) also pose challenges for analytical method development and validation.
- **Long Development Times**: A separate analysis of FDA data from 2015 to 2017 revealed that an orphan drug designation does not contribute to accelerated approvals. Longer development times between receipt of designation and product launch causes increase in unmet medical needs. It was found that it can take 10 or more years — and sometimes more than 20 — from receipt of orphan drug designation to marketing approval, with four to eight years the most common timeframe
- **Technical Challenges**: Rare diseases that affect limited patient populations and have not been extensively studied or which does not have well laid natural history study data can pose significant research and development challenges for companies looking to identify new drugs to treat them

8. Orphan Drug Pricing

There has always been a lag between patient needs and available treatment. Along with that, rising cost of treatment, lack of adequate insurance coverage and premium pricing of drugs are contributing to bigger issues. The primary health care cost factors associated with the expense of treating rare indications are inpatient care and cost of prescription medications. A small percentage of patients who require a lot of treatment resources often cause the average treatment cost to be skewed. In addition, the significant degree of variation in healthcare needs, as well as the kind and cost of therapy, makes it difficult to conclude the incurred cost per patient or as per rare indication.

➢ **Orphan Drugs Price Rise Factors**

- **Concentration of research on specific therapeutic class**

Oncology contributed to *32% of orphan designations while other individual therapeutic classes hardly crossed 10%*. As a result, only oncology has shown growth in orphan drug designation which caused overall growth in orphan drug market. The concentration of research in the field of oncology makes it the rapidly growing and highly lucrative therapeutic class. As a result of this other areas of rare diseases are not given much attention. This results in low availability of treatment for certain disorders thereby raising the overall cost due to demand of drugs.

- **Less Payer coverage and increasing pressure on insurance companies for increasing cover**

Due to recent scientific advances and regulatory flexibility, there are significant number of orphan drugs awaiting approval and more are in the budgetary pipeline of pharmaceutical companies. *Orphan Drugs being good revenue generator segment, there is increased focus of manufacturers and sponsors to invest more*. Previously, rare disease treatment coverage by payers was not significant and there was no clear roadmap for the payer companies for addressing rare disease treatment coverage. Payers are now confronted with additional issues in the management of orphan pharmaceuticals because of demand from patient advocacy organizations, clinicians, and plan sponsors to increase access and reduce healthcare

spending. There has been no new policy brought in by the payer companies to address rare disease coverage and it is expected to follow pathways like that of non-orphan and speciality drugs. The *covered benefits may not be able to address needs as per specific orphan conditions which may not reflect as an efficient price control or treatment benefit outcome*.

- **Lack of competition due to Orphan Drug Exclusivity**

The FDA is not permitted to approve a new brand name or generic medicine application for the same product and for the same rare disease indication once a product has been granted orphan drug exclusivity of seven years. However, a *medicine can be approved for use in more than one indication, and no restriction is there on drugs that can be authorized for a given disease*. Patients may profit from the availability of more therapy alternatives and price reductions brought about by increased competition if more medicines are allowed for certain rare diseases. But *non availability of branded alternatives still causes monopoly of specific brands* thereby reducing the perceived benefit of therapy alternatives. But removing the exclusivity clause may remove a key incentive for investment in orphan drug research.

- **Higher cost of perceived value of treatment**

Individual cost of treatment is highly dynamic since many biologic agents, and expensive orphan drugs, fall under the category of "tier 4" drugs, for which patients are required to *cover between 20 and 33 percent of total costs under the increasingly prevalent private coinsurance-like plans in the United States*. Although more orphan pharmaceuticals enhance patients' health and quality of life, the expense of newer drugs restricts access of patients to quality healthcare.

- **Non-alignment of incentives with perceived societal benefits**

With new diagnostic techniques and understanding of specific causes of disease there have been rise in the number of orphan drug patients. Whereas supply of effective treatment is still not as expected. The available treatments combined with rising inflation cost cause significant financial burden on patients, government aided healthcare programs and private insurers. Lack of alignment of research grants and incentives with societal demographic and economic aspect has caused benefits to be skewed in favor of companies and neglected patient priorities. It is important to address every aspect of regulatory, clinical, and economic landscape to ensure rare disease patients get access to quality, affordable and effective treatments.

- **Lack of clinical data to assess cost benefit effectiveness**

There is lack of information about overall health status of a patient and pre-market cost strategy of a company related to Orphan Drugs. Due to this proper cost-benefit effectiveness assessment is not of proper quality. Thus, it is still crucial to weigh the costs of economic incentives on orphan development initiatives against their overall advantages and enhancements in treatment outcomes. If not, there is a chance of exacerbating market imperfections and maintaining inefficiencies. Given the diversity of the medications authorized for orphan indications, study results should be evaluated with caution.

- **Freedom of pricing and minimal competition**

Drug manufacturers in the US negotiate with organizations like Medicaid, the Veterans Health Administration, and Pharmacy Benefit, but can set own initial prices. Additionally, competition between manufacturers has little impact on regulatory standards compared to price caps. Due to the challenges in proving therapeutic equivalence and the rarity of large-scale trials by generic manufacturers, many orphan medications, particularly biotechnology products, have minimal competition even when exclusivity restrictions expire. Since these *generics are still expensive with prices 20-25% less expensive* than *branded biologics*, whereas traditional generics are *75-85% less expensive* than branded pharmaceuticals, the influence of biogeneric medications on prices of orphan drugs may be minimal. Additionally, the lack of a clearly defined FDA clearance process has prevented the few biogeneric/biosimilar medications from entering the American market.

➢ **Proposals to address pricing issue**

- **Adopt best practices from other regulated markets**

Initiatives from Japan could be taken into consideration to solve the issue of commercial pharmaceuticals that have benefited from various incentives for orphan drug development (such as research and development support funds, fee waivers, and tax credits). Pharmaceutical companies in Japan are required to charge a 1% sales tax on orphan drugs with yearly gains of more than 100 million yen until the obtained government subsidies have been returned. This provision has not caused any roadblock in orphan drug development and there has been approval of almost 100 orphan pharmaceuticals in the twelve years since the policy's enactment in 1993. Incentives given to one R&D company is returned by marketing company. This tax clause might potentially be transferrable. Profitable *orphan pharmaceuticals would no longer receive government funding in this fashion, but less successful orphan drugs would continue to receive incentives.*

- **Redefine Rare Disease and Orphan Drugs**

Senators Metzenbaum and Kassebaum planned to introduce legislation that would clarify the definition of an orphan drug at the start of the 1990s. The terms "orphan medication" and "rare disease" need to be redefined given the current state of medical technology, which heralds the *advent of customized therapy, and the ageing of the population*, which causes the *emergence of rare new diseases*. By pursuing this goal, it would be possible to limit the therapeutic market for orphan pharmaceuticals, generate more uniform investment distribution among different therapeutic areas of rare diseases, and manage the number of indications for each condition.

- **Development of patient registry funded by Federal Government**

To address the needs of patients, doctors, and payers and to effectively analyze the cost effectiveness of therapies, more sophisticated systems for collecting and analyzing observational data are required. These *data systems ought to be created to be able to record patient-reported outcomes that represent therapeutic effects on the patient and their families.* By supporting rare condition registries, the federal government may speed up efforts to improve evidence generation with the aid of illness and patient groups.

- **Orphan Drug price reduction through price control**

Spending on orphan medications has risen with the expansion of orphan drug development. Increases in orphan medication volume and their greater cost are clearly visible in available data published by companies and market research agencies. The *average annual orphan medication cost in 2017 was 25 times higher than that of non-orphan drugs*. A further analysis revealed that there was *huge gap in pricing of top 100 medicines* by sales based on *treated indications [(US$ therapy for orphan drugs was 4.5 times that of nonorphan drugs, at $150,854 vs. $33,654 per patient]*. This gap needs to be addressed to effective price control measures.

- **Expansion of outcome-based contracts**

A treatment's payment may be partially or entirely based on how much the patient benefits from it under outcomes-based contracts. *Manufacturers and payers are required under these contracts to come to an agreement on a list of outcomes that can be measured* and to monitor those outcomes to resolve any disputes. It is a difficult exercise to assess and implement these suggestions. Managing treatment coverage and indirectly the pricing is based on real world data. It is adopted by payers because this is based on *increased clarity on clinical outcome and addresses effectiveness of treatment based on live evidence*. But the current design of coverage models is not effective enough to impact pricing drastically and treatment affordability may not be addressed on an immediate basis.

- **Adoption of volume-based contracts**

Volume-based contracts can be another strategy that could help the commercialization of uncommon products. While the *government has historically utilized volume-based contracts* to buy huge quantities of pharmaceuticals (such as vaccines), a *similar strategy might be used*

in the orphan drug market. The *government or a consortium of private payers might actively bargain to buy adequate orphan drugs* to cover most or all qualified patients with a specific rare ailment under this scenario. This will provide a clear picture of effected population and data around treatment coverage. A *price specific to the concerned orphan indication could be established by the government or a private body consortium* under the contract. *Utilization based pricing is one of the key features of volume-based contracts*. Prices of orphan drugs can be *high on launch can be gradually reduced as and when market expands* due to increased patient uptake, new dosage availability, new delivery form of similar treatment etc.

- **Considering Indication-based pricing**

Orphan indication pricing of medicines *typically remain expensive* even if there are additional indication approvals present for those medicines. If indication-based pricing could be successfully adopted, payers would be able to bargain for reduction of prices for more common indications or for medications with less therapeutic value. *Pricing can be fixed by independent assessment body based on clinical effectiveness on concerned indications*. Although indication-based pricing would boost access, there is a chance that *manufacturers could raise costs for high-value indications*, which could result in increased patient cost sharing for rare diseases. *Present cost structure and supply chain scenario* in the United States may prove *ineffective in controlling the prices* and patients with rare indications may end up paying more without getting the required cost benefit.

- **Pursuing value-based pricing**

Value-based pricing control may add to other policies aiming to rationalize incentives and enhance treatment affordability, as was mentioned above in relation to several policy choices. There are a *variety of options, such as the use of reference pricing based on international standards or pricing based on criteria* of effectiveness of costing and pricing algorithms recommended by value assessment organizations like the Institute for Clinical and Economic Review (ICER). The methodology for v*alue-based price-setting is dynamic and based on new evidence and outcomes,* which is one advantage of this strategy. Additionally, value-based price setting encourages *investment in development of evidence tracking methodologies* to show the clinical benefits of novel therapeutics. It also offers attractive *market rewards for breakthrough products*. *Policymakers must decide whether to apply different requirements for cost-effectiveness to medications* that treat rare and ultra-rare disorders when adopting a value-based pricing system for orphan drugs.

- **National treatment benefit implementation for rare diseases**

Insurance *payments rely on the existence of patient pools that are sizable enough* to track the associated risks and distribution of diseases. These pools are very large for rare diseases in order to address the claim shock of small insurers for large number of patients with rare disorders. The risk of *unanticipatedly expensive orphan drug therapies is being managed by numerous national health plans* by developing insurance products. This strategy has received support from some federal policymakers, one example being Embarc protection plan by Cigna. In addition to enabling patients to obtain therapies without any *individual costs, the premium structure protects employers from the burden of an unplanned high-cost treatment*. Even though these initiatives have little commercial implementation, policy makers can consider legislating the same. A single patient pool for all recognized rare ailments can be created. Such a program can specifically address orphan product, cell and gene therapy payouts. This will provide more uniform coverage and will allow payers to provide support for relevant products and therapies more efficiently.

- **Patient Assistance Programs (PAP's)**

Many patients find great value in patient assistance programs, which are often the cornerstone of orphan medication company marketing campaigns. The level of financial aid varies depending on the patient's specific income and could involve other organizations. *For patients using imiglucerase, alglucerase (Ceredase), laronidase (Aldurazyme), agalsidase beta (Fabrazyme), and alglucosidase alfa, Genzyme Corporation, for instance, offers the*

Charitable Access Program (*Myozyme*). These initiatives provide eligible patients with a limited supply of free medications.

NORD Initiatives: *National Organization of Rare Diseases, help covered patients with their insurance premiums and co-payments. 34 patient support initiatives* that NORD manages on behalf of orphan medicine producers are listed on its website. As part of RareCare®, since 1987, NORD has aided programs to help patients obtain lifesaving or life-sustaining medication they could not otherwise afford. These programs provide medication, financial assistance with insurance premiums and co-pays, diagnostic testing assistance, and travel assistance for clinical trials or consultation with disease specialists. Below listed are few *live* programs:

Table 4: Examples of Patient Assistance Programs from NORD

Source: *Patient Assistance Programs, Medication Specific Assistance Programs*. NORD (National Organization for Rare Disorders). https://rarediseases.org/for-patients-and-families/help-access-medications/patient-assistance-programs-2/

Program Name	Status	Benefits	Email
Acute Lymphocytic Leukemia	Temporarily Waitlisting Patients	Premium Assistance, Co-Pay Assistance Program	all@rarediseases.org
Alpha-1 Antitrypsin Deficiency	Temporarily Waitlisting Patients	Premium and Co-Pay Assistance Program	alpha-1@rarediseases.org
Atypical Hemolytic Uremic Syndrome	Accepting Applications	Premium Assistance, Co-Pay Assistance, Medical Assistance, Emergency Relief Assistance	ahus@rarediseases.org
Barth Syndrome	Accepting Applications	Emergency Relief	Barthsyndrome_assist@rarediseases.org
Batten Disease	Accepting Applications	Emergency Relief	BattenDisease@rarediseases.org
		Clinical Trial Support for Neurogene Batten Disease CLN5 trial	BattenDisease@rarediseases.org
Bile Acid Synthesis Disorders	Accepting Applications	Premium Assistance, Co-Pay Assistance, Medical Assistance	BileAcidSynthesis@rarediseases.org
Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)	Accepting Applications	Co-Pay Assistance, Emergency Relief Program	BPDCN@rarediseases.org
		Travel & Lodging Assistance Program	BPDCN@rarediseases.org
Cerebrotendinous Xanthomatosis (CTX)	Accepting Applications	Premium Assistance, Co-Pay Assistance, Medical Assistance	ctx@rarediseases.org
Chronic Granulomatosis Disease (CGD)	Accepting Applications	Emergency Assistance, Co-Pay Assistance, Medical Assistance	CGDassist@rarediseases.org
Classical Homocystinuria	Accepting Applications	Medical Assistance	HCU@rarediseases.org
Clear Cell Sarcoma		Clinical Trial Travel & Lodging Assistance	sarascure_ccstravel@rarediseases.org
Cushing's Syndrome	Accepting Applications	Premium Assistance, Co-Pay Assistance,	cushings@rarediseases.org

		Medical Assistance	
Cystinosis	Accepting Applications	Emergency Assistance, Co-Pay Assistance, Medical Assistance	cystinosis_assist@rarediseases.org
Cystinuria	Accepting Applications	Premium Assistance, Co-Pay Assistance, Medical Assistance	cystinuria@rarediseases.org
Duchenne Muscular Dystrophy	Temporarily Waitlisting Patients	Co-Pay Assistance, Medical Assistance	DMD@rarediseases.org
		Clinical Trial Travel & Lodging: PTC 124-GD-016-DMD	DMD@rarediseases.org

9. Orphan Drugs: A New Commercial Opportunity

Treatments for rare diseases can be quite profitable. The revenue generating potential of orphan vs non-orphan medications may be influenced by several factors, in addition to the statutory incentives for orphan drug development: Private health plans typically have little bargaining power when attempting to negotiate rates for pricey biotechnology medications, many of which are orphan pharmaceuticals.

This can be due to:

- The lack of competition in terms of R&D of drugs, thereby providing leverage to sponsor in terms of discounting and price fixing
- Treatment plan covers limited volume of drug usage, causing reduction in negotiating power over pricing based on volume of usage
- Orphan pharmaceuticals are currently a profitable business prospect, with *43 brand-name medications having orphan designations and having global annual sales of more than $1 billion USD*. 18 of these were only given orphan medication approval in the US. 1*1 of these 18 medications were developed during the seven years of market exclusivity* for orphan drugs before becoming best in the market

In comparison to non-orphan medications, the *economic and investment justification for developing and commercializing orphan drugs appears to be stronger*. As the target patient population for orphan drugs is low, this is an important point to focus on. The favorable economics for orphan medications may be due to several important variables such as:

- Orphan drug trials can be of shorter duration *(3.9 years) as compared to that of non-orphan drugs (5.4 years)*
- Approval of orphan drugs from regulatory filing perspective is *higher (93% chance of success) as compared to non-orphan drugs (88%)*

A comparative study of treatment prices of orphan against non-orphan drugs can provide valuable points of pricing that can be used by sponsors and manufacturers to develop more effective expenditure plan for R&D of orphan drugs. The study should focus on treatments with comparable treatment characteristics between orphan and non-orphan drugs.

5 List of US FDA Approved Orphan Drugs related to Blood Disorders

Generic Name	Trade Name	Date Designated	Orphan Designation	Marketing Approval Date	Exclusivity End Date	Patent Submission	Patent Expiry	Sponsor Company
Cromolyn Sodium	Gastrocrom	03-08-1984	Treatment of mastocytosis.	22-12-1989	22-12-1996	Patent expired	Patent Expired	Fisons Corporation
Epoprostenol	Flolan	25-09-1985	Treatment of primary pulmonary hypertension.	20-09-1995	20-09-2002	No patent information	No patent information	Glaxo Wellcome Inc.
Hydroxyurea	Droxia	10-01-1990	Treatment of patients with sickle cell anemia as shown by the presence of hemoglobin S.	25-02-1998	25-02-2005	No patent information	No patent information	Bristol-Myers Squibb Pharmaceutical Research Institute
Desmopressin Acetate	DDAVP	22-01-1991	Treatment of mild hemophilia A and von Willebrand's disease.	03-07-1994	03-07-2001	No patent information	No patent information	Ferring Pharmaceuticals, Inc.
Aprotinin	Trasylol	17-11-1993	For prophylactic use to reduce perioperative blood loss and the homologous blood transfusion requirement in patients undergoing cardiopulmonary bypass surgery in the course of repeat coronary artery bypass graft surgery, and in selected cases of primary c	29-12-1993	29-12-2000	Patent expired	Patent Expired	Bayer Corporation
Sodium Phenylbutyrate	Buphenyl	22-11-1993	Treatment of urea cycle disorders: carbamylphosphate synthetase deficiency, ornithine transcarbamylase deficiency, and arginiosuccinic	30-04-1996	30-04-2003	No Patent Information	No Patent Information	Medicis Pharmaceutical Corp.

			acid synthetase deficiency.					
Epoprostenol	Flolan	22-03-1999	Treatment of secondary pulmonary hypertension due to intrinsic precapillary pulmonary vascular disease.	14-04-2000	14-04-2007	No patent information	No patent information	GlaxoSmithKline
L-Glutamine	Endari	08-01-2001	Treatment of sickle cell disease	07-07-2017	07-07-2024	No patent information	No patent information	Emmaus Medical, Inc.
Deferiprone	Ferriprox	12-12-2001	Treatment of iron overload in patients with hematologic disorders requiring chronic transfusion therapy	30-04-2021	30-04-2024	**5 patents: Submission Dates** 31-01-2019 06-10-2015 10-03-2021 07-10-2021 21-06-2022	**5 patents: Expiry Dates** 26-10-2029 26-10-2029 25-10-2038 25-10-2038 25-10-2038	Chiesi USA, Inc.
Deferiprone	Ferriprox	12-12-2001	Treatment of iron overload in patients with hematologic disorders requiring chronic transfusion therapy	14-10-2011	14-10-2018	**5 patents: Submission Dates** 31-01-2019 06-10-	**5 patents: Expiry Dates** 26-10-2029 26-10-2029 25-10-2038 25-10-2038	Chiesi USA, Inc.

						2015 10-03-2021 07-10-2021 21-06-2022	25-10-2038	
Deferiprone	Ferriprox	12-12-2001	Treatment of iron overload in patients with hematologic disorders requiring chronic transfusion therapy	19-05-2020	30-04-2024	**5 patents: Submission Dates** 31-01-2019 06-10-2015 10-03-2021 07-10-2021 21-06-2022	**5 patents: Expiry Dates** 26-10-2029 26-10-2029 25-10-2038 25-10-2038 25-10-2038	Chiesi USA, Inc.
Deferasirox	Exjade; Jadenu Sprinkles	21-11-2002	Treatment of chronic iron overload in patients with transfusion-dependent anemias	18-05-2017	23-07-2023	No patent information	No patent information	Novartis Pharmaceuticals Corp.
Multi-Vitamin Infusion Without Vitamin K	M.V.I.-12	03-08-2004	Prevention of vitamin deficiency and thromboembolic complications in people receiving home parenteral nutrition and warfarin-type anticoagulant therapy	09-09-2004	09-09-2011	No patent information	No patent information	Mayne Pharma (USA) Inc.

Eltrombopag	Promacta	05-05-2008	Treatment of idiopathic thrombocytopenia purpura	20-11-2008	20-11-2015	**16 patents Submission on dates** 07-12-2011 10-07-2014 10-07-2015 21-09-2015	**16 patents: Expiry dates** 20-11-2022 20-05-2023 13-07-2025 13-01-2026 21-05-2023 21-11-2023 01-08-2027 (5) 01-02-2028 (5)	Novartis Pharmaceuticals Corp.
Methylene Blue0.5%	ProvayBlue	18-12-2012	Treatment of hereditary and acquired methemoglobinemia	04-08-2016	04-08-2023	No patent information	No patent information	Provepharm SAS
Defibrotide	Defitelio	21-05-2013	For the treatment of hepatic veno-occlusive disease	30-03-2016	30-03-2023	**2 patents: Submission Dates** 20-08-2021 17-02-2022	**2 patents: Expiry Dates** 22-06-2032 22-06-2032	Jazz Pharmaceuticals, Inc.
Sodium Phenylbutyrate	Pheburane	06-06-2013	Treatment of urea cycle disorders	17-06-2022	No information	No Patent Information	No Patent Information	Medunik Canada Inc
Hydroxycarbamide (Hydroxyurea)	Siklos	24-07-2013	Treatment of sickle cell disease in patients under 18 years of age	21-12-2017	21-12-2024	No patent information	No patent information	Addmedica Laboratories

Eltrombopag	Promacta	11-08-2013	Treatment of aplastic anemia	26-08-2014	26-08-2021	**6 patents Submission dates** 21-09-2015 (6)	**6 patents: Expiry dates** 20-11-2022 20-05-2023 13-07-2025 13-01-2026 21-05-2023 21-11-2023	Novartis Pharmaceuticals Corp.
Eltrombopag	Promacta	11-08-2013	Treatment of aplastic anemia	16-11-2018	16-11-2025	**6 patents: Submission dates** 05-04-2019 (6)	**6 patents: Expiry dates** 20-11-2022 20-05-2023 13-07-2025 13-01-2026 21-05-2023 21-11-2023	Novartis Pharmaceuticals Corp.
Pegcetacoplan	Empaveli	20-04-2014	Treatment of paroxysmal nocturnal hemoglobinuria	14-05-2021	14-05-2028	**8 Patents Submission Dates** 09-06-2021 (6) 16-07-2021 (1) 29-04-2022 (1)	**8 Patents Expiry Dates** 12-04-2027 (2) 18-11-2027 (1) 15-11-2033 (3) 02-08-2033 (1) 09-04-2038 (1)	Apellis Pharmaceuticals, Inc.

Deferasirox	Exjade; Jadenu Sprinkles	24-02-2015	Treatment of chronic iron overload in alpha-thalassemia	18-05-2017	No information	No patent information	No patent information	Novartis Pharmaceuticals Corporation
Deferasirox	Exjade; Jadenu Sprinkles	24-02-2015	Treatment of chronic iron overload in alpha-thalassemia	23-01-2013	23-01-2020	No patent information	No patent information	Novartis Pharmaceuticals Corporation
Fostamatinib Disodium Hexahydrate	Tavalisse	25-08-2015	Treatment of immune thrombocytopenic purpura	17-04-2018	17-04-2025	**14 Patents Submission Dates** 16-05-2008 (13) 23-02-2022 (1)	**14 Patents Expiry Dates** 04-09-2026 28-03-2026 12-06-2026 17-06-2026 (4) 19-01-2026 (3) 24-11-2030 06-11-2028 27-07-2032 (2)	Rigel Pharmaceuticals, Inc.
Voxelotor	Oxbryta	29-12-2015	Treatment of sickle cell disease	17-12-2021	25-11-2024	**8 Patents Submission Dates** 14-01-2022 (8)	**8 Patents Expiry Dates** 28-12-2032 (4) 29-01-2034 (1) 06-02-2035(2) 02-12-2036	Global Blood Therapeutics, Inc.

							(1)	
Voxelotor	OXBRYTA	29-12-2015	Treatment of sickle cell disease (SCD).	25-11-2019	25-11-2026	**9 Patents Submission Dates** 19-12-2019 (6) 27-08-2020 (1) 19-11-2020 (1) 23-06-2021 (1)	**9 Patents Expiry Dates** 28-12-2032 (4) 29-01-2034 (1) 06-02-2035(2) 02-12-2036 (1) 12-10-2037 (1)	Global Blood Therapeutics, Inc.
Deferasirox	Exjade; Jadenu Sprinkles	21-11-2022	Treatment of chronic iron overload in patients with transfusion-dependent anemias	11-02-2005	11-02-2012	No patent information	No patent information	Novartis Pharmaceuticals Corp.

i. **Key findings:**

✓ Orphan Drug development in US has seen significant improvement post enactment of Orphan Drug Act in 1983

✓ There were discoveries of many drugs across multiple therapeutic areas benefiting patients suffering from rare diseases. This has been made possible by economic benefits, research grants, free pricing and constant collaboration between FDA, researchers, sponsors, pharmaceutical companies, and patient organizations

✓ FDA approval processes which include fast track approval and designation is encouraging participants from both industry and academia to invest more in R&D of orphan drugs

✓ Commercial viability regarding cost allocation and pricing of orphan drugs have undergone significant changes considering factors like competition, usage, target population and drug type concentration tilting economic balance in favor of sponsors primarily biotechnology companies

✓ Patient organizations have consistently played an important role in spreading awareness, participating in research studies, and pricing strategies

✓ Pricing remains high making treatment inaccessible to majority of patients. Insurance pay-outs are not sufficient to cover the expenses with 20%-33% of costs managed by patients

✓ Focus should be more on development of new molecular or biological entity for orphan treatment rather than repurposing of existing therapies

✓ Initiatives should be taken to address the cost factor without impacting the quality of research and drug product

- Free pricing to be encouraged till the marketed drugs become profitable
- Pharmaceutical pricing regulation to be brought in to control long term pricing
- Payback of subsidy to be introduced for profitable drugs to further investments in other drugs

✓ Economic benefits should move towards patients as well to make the treatments more affordable and ensure increased penetration of therapeutics to a larger global population

References:

1. Patient Registries and Rare Diseases, Richard Gliklich, MD, Michelle Leavy, applied clinical trials, Mar 1, 2011 available at, http://www.appliedclinicaltrialsonline.com/appliedclinicaltrials/article/articleDeta il.jsp?id=711269
2. Alissa Lim, Noel Cranswick, clinical trials, ethical issues and patient Recruitment: an Australian perspective. Paed Perinatal Drug Ther 2003; 5: 183– 187.
3. Roger L. Kaspar, Challenges in Developing Therapies for Rare Diseases Including Pachyonychia Congenita. J Investig Dermatol Symp Proc 10:62 –66, 2005.
4. S. P. Kalantri , Anaesth in Ethics in clinical research by,2003; 47 (1) : 30-32.
5. FDA Regulatory Affairs, The Development of Orphan Drugs, Marlene E. Haffner page numbers 195-207.
6. European Medicines Agency, Orphan drugs and rare diseases at a glance, EMEA/290072/2007, 3 July 2007.
7. Principles for research using the human beings as participants, ethical guidelines for biomedical research on human participants, available at http://whoindia.org/LinkFiles/HSD_Resources_Ethical_Guidelines_for_Biomedic al_Research_on_Human_Subjects.pdf
8. Principles for research using the human beings as participants, ethical guidelines for biomedical research on human participants.
9. ethical issues during the conduct of clinical trials, FDA Regulatory Affairs, The Development of Orphan Drugs, Marlene E. Haffner page numbers page numbers 207.
10. List of orphan drugs in Europe with European orphan designation and European Marketing Authorisation, available at, http://www.orpha.net/orphacom/cahiers/docs/GB/list_of_orphan_drugs_in_europ e.pdf
11. List of orphan drugs in Europe with European market authorisation without prior orphan designation in Europe, available at, http://www.orpha.net/orphacom/cahiers/docs/GB/list_of_orphan_drugs_in_europ e.pdf