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THE ORPHAN DRUG ACT: INCENTIVES, CHALLENGES, AND MARKET TRENDS

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ABSTRACT: Orphan drugs are used to treat rare diseases that affect fewer than 200,000 people in the United States. Development and approval of orphan drugs are challenging due to the limited patient population and substantial development costs; the U.S. Food and Drug Administration (FDA) has established several programs, such as the Orphan Drug Designation program and Orphan Product Grants program to encourage the development of medications that treat rare diseases, the rare pediatric disease voucher program supports research and growth of rare diseases that affect pediatric populations, the humanitarian use device program regulates medical devices associated with rare diseases, the main aim of these incentives is to provide financial and regulatory support to sponsors. Overall, the regulatory framework in United States offers a supportive environment for drug manufacturers in developing and approving orphan products; these initiatives ensure that patients with rare diseases have access to safe and effective treatments. United States is one of the top leaders in developing orphan drugs and continues to play a critical role in the global effort to bring new therapies to patients with this rare disease.

INTRODUCTION: Orphan drugs treat rare diseases or disorders that occur in less than 200,000 people in the U.S.; orphan drugs are drugs used in the prevention, treatment, and diagnosis of rare diseases (diseases with less available information) or diseases that do not commonly occur [1]. The drugs eligible for orphan drug designation are new molecular entities (drugs newly developed for treating certain rare diseases), secondary indications (expansion of already existing symptoms, and any newly developed formulations [2].

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In 1983, The Orphan Drug Law Act (ODA) was passed by the United State Congress because –

1. There were many diseases and conditions, such as Huntington's disease, Tourette syndrome, and myoclonus which affected only a few individuals and were rare in the United States.
2. Pharmaceutical companies did not develop drugs for rare diseases.
3. The drugs for rare diseases are named "Orphan Drugs."
4. The pharmaceutical companies were not that interested in developing orphan drugs as the sales generated were less than the cost of producing the drug.
5. Bring necessary changes to federal laws in reducing the developing costs of orphan drugs and providing financial incentive.

6. It is in public interest to develop orphan drugs [3, 1].

The Office of Orphan Products Development (OOPD) under the FDA evaluates and develops orphan drugs and new treatments for rare diseases; it considers the information submitted by developers and determines if drugs, biologics, or medical devices meet the criteria for research. The OOPD also collaborates with research communities, rare disease organizations, government agencies, industry, and patient groups to evaluate issues related to rare diseases.[4]

The Office of Orphan Products Development (OOPD):

1. Evaluates the application type submitted (e.g., orphan drug, rare pediatric disease drug, or humanitarian use device designation).
2. Grant orphan drug status to drugs and biologics intended to diagnose treat or prevent rare diseases that affect fewer than 200,000 people in U.S.
3. Identify medical devices used to treat or diagnose a rare disease affecting fewer than 8,000 people in U.S.
4. Works with the Office of Pediatric Therapeutics to evaluate specific rare pediatric disease designations for drugs and biologics.
5. Provide grants for clinical trial funding and natural history studies for rare disease product development.
6. Provide grants for pediatric medical device development.
7. Provide grants to determine and characterize the history of rare neurodegenerative diseases and aid in developing new treatments.

Manufacturers were granted incentives under the Orphan Drug Act to develop drugs for rare diseases. Since then, 600 drugs have been approved by the FDA to treat rare diseases, with cancer being the main category for which the greatest number of orphan approvals happened [5].

The Act Provides Specific Incentives to Orphan Drug Manufacturers, such as:

Market Exclusivity up to Seven Years: Orphan drug developers get market exclusivity of seven years to reimburse their development costs; during the market exclusivity period, the FDA cannot approve an abbreviated new drug application (ANDA) or a new drug application (NDA) for the same rare disease indication. The drug can get approval for another indication during this period. The pricing of orphan drugs is quite expensive as the developer wishes to retrieve the development cost from a small population of patients; as rare diseases have limited treatment options and medicines available in the market, they are willing to pay for these expensive orphan drugs [6].

Tax Credits for Clinical Trials: The tax credit incentive was introduced in 1983, the drug developers were given tax incentives of up to 50% to develop drugs for rare diseases, which led to the development of more than 500 drugs for rare diseases. During the U.S. tax reform package, the tax credit was decreased to 27.5%, and as of now, orphan drugs receive a reduced tax credit of 25% for orphan drugs. The Internal Revenue Service (IRS) gives tax credits, not the FDA [6, 7].

Prescription Drug User Fee Act (PDUFA) Exemption: The FDA collects a user fee for any drug or biologic application submitted to it for license approval; the fee cost is usually around $2.2 million, and the FDA does not begin the review until the fee is paid, orphan drugs are not subject to application fee under the act unless the drug is used for another indication that does not fall under rare diseases. The drug applicant must notify the FDA that the application qualifies under an orphan exemption and submit FDA form 3397 [8, 9].

TABLE 1: A BRIEF DESCRIPTION OF THE ORPHAN DRUG ACT AND ITS INCENTIVES

Element	Description	Impact
Rare diseases, Orphan drugs	A disease or disorder that occurs in less than 200,000 people in the U.S. The drugs used in the prevention, treatment, and diagnosis of rare diseases. (Diseases that do not commonly occur)	The main aim of The Orphan Drug Act is to provide incentives to drug manufacturers to develop orphan drugs for treatment of rare diseases

Market Exclusivity	Orphan drug developers get market exclusivity of seven years to reimburse their developmental costs	A chemical gets market exclusivity for 5 years in the U.S., for orphan drugs the exclusivity period is 7 years during which market authorization is not provided for generic drug for rare disease
Tax credits	Tax incentive upto 25% is given to orphan drug manufacturers for orphan drugs	The lowering of tax credit is beneficial for drug manufacturers who without this incentive may not be able to develop drugs and programs for rare diseases
Prescription Drug User, Fee Act (PDUFA) exemption	For rare diseases FDA does not collect the PDUFA fee from the manufacturer	The development cost of rare diseases is very expensive, this user fee exemptions allows manufacturers to enable therapies for rare diseases faster
Grant Programs	Different grant programs are provided by FDA to develop and help aid orphan drug manufacturers in conducting clinical trials, developing rare pediatric orphan drugs, enabling research of rare neurodegenerative diseases	These grant programs encourage orphan drug development for rare diseases

Source: Cheung R, Kohler J, Illingworth P. Health Law Journal. 2004; NORD Impact of the Orphan Drug Tax Credit on treatments for rare diseases 2015; FDA.gov, oig.hhs.gov [10]

FDA Incentive Programs for Orphan Drug Development:

Rare Pediatric Disease Priority Review Voucher Program: FDA evaluates if the drugs or biologics meet the definition of a rare pediatric orphan drug, a drug used to treat a rare disease or condition that is life-threatening in children aged 0 through 18 years old [11].

Under section 529 of the Federal Food, Drug, and Cosmetic Act, priority review vouchers are awarded to sponsors of rare pediatric disease by FDA if product application meets the required criteria. To be eligible for this voucher, the drug must be-

1. Approved for a rare pediatric disease or disorder.
2. In preventing a life-threatening severe manifestation of the disease that is affecting children.

Sponsors must work with CBER or CDER to ensure that the drug is studied in a way that establishes safety and efficacy for a rare pediatric indication [12].

Humanitarian Use Device (HUD) Program: is a program that designates medical devices intended to treat or diagnose a disease or condition that affects 8,000 individuals or fewer in the U.S. (or) a medical device designed to benefit patients in treatment or diagnosis of a disease that affects not more than 8,000 people in the U.S [13].

The HUD program came into action to create an alternative pathway for getting market approval for medical devices that people with rare diseases use. To obtain a HUD application, the sponsor must describe;

1. The condition or disorder that the medical device is proposed to treat.
2. Submit evidence that the disease incidence is not more than 8000 in the target population.
3. Give device description and scientific rationale for using the said device in treating or preventing a rare disease.

HUD does not have financial incentives but is eligible for an alternative marketing pathway known as Humanitarian Device Exemption (HDE) pathway, which is less stringent than the Pre-Market Approval (PMA). Within 45 days of receiving a HUD application, OOPD will approve, disapprove, or ask for additional information related to the application [14].

The FDA Provides Grant Programs to Orphan Drug Sponsors for Rare Diseases; These Grant Programs are:

Orphan Products Grant Program: Also known as the Orphan Products Clinical Trials Grant Program, supports clinical trial funding and encourages natural history studies to help the development of safe and effective drugs that treat rare diseases. The orphan drug grant program came

into force in 1983 and has since helped approve more than 80 products that treat rare diseases [15].

Natural History Studies was introduced in 2016 to help understand and address unmet medical needs of patients suffering from rare diseases; as rare diseases affect only fewer populations, there is significantly less knowledge or understanding of these diseases, and very little research is done to understand and study orphan diseases, to bridge this gap, understand day-to-day needs. Unmet needs of rare diseases, this program was funded by the FDA [16].

The Pediatric Device Consortia (PDC) Grants Program: This program provides funding to develop medical devices for use in Pediatric populations; children differ from adults in size, growth, body chemistry, and disease propensity. Due to this, only a few medical devices are approved and developed for pediatric use. The pediatric consortia grants program also helps in establishing a platform where different services such as animal testing, intellectual property rights awareness, grant writing for pediatric medical devices is provided. FDA also provides monetary funding for this program [17].

The Rare Neurodegenerative Disease Grant Program: the program came into action when FDA enacted the Accelerating Access to Critical Therapies for ASL; the main aim of this grant program is to stimulate the research and development of drugs that can treat, diagnose, mitigate, or cure ALS and other rare neurodegenerative disorders in both adults and pediatric populations [18].

Data Requirements of an Orphan Drug Designation Request [19, 20]:

Administrative Information: the drug developer must include an orphan drug application statement in their form, and the sponsor must identify the disease for which an orphan drug status is requested. The sponsor must provide all the information according to 21 CFR 316.20(b)(2). The sponsor must mention the chemical name, generic name, or trade name for the orphan drug in the application.

Explain the disease/Condition: The sponsor must clearly state which rare disease or condition their drug intends to treat; determining the affected population's size is critical in developing an orphan drug.

Scientific Understanding: scientific understanding of certain diseases may change over time. Therefore, a condition doesn't need to remain orphan-designated; it may evolve.

Ex–OOPD grouped lymphoma to be a distinct disease, and further studies on it led to classifying lymphoma into different types; now, each has its own disease entity.

Determination of the disease: The FDA must determine what illness or condition the orphan drug is treating; the sponsor must submit sufficient information on the mechanism of action, disease pathophysiology, and etiology of the disease to understand whether the orphan drug aims to treat the rare disease or just a symptom or complication of the rare disease.

Ex- pancreatic enzymes are used to treat pancreatic insufficiency in cystic fibrosis; the sponsor may apply for an orphan drug status to treat it regardless of the disease-causing it.

Sufficient Scientific Rationale: sponsor must provide adequate scientific reasoning to the FDA to support the use of the drug in the diagnosis, treatment, or prevention of a rare condition; the information provided must establish the basis for drug effectiveness. Data related to *in-vivo* and *in-vitro* clinical studies, the drug's mechanism of action, *etc*., must be provided.

Additional Information: must be provided to the FDA if the same drug has already been approved for use in the same indication. The same drugs are not identical; they are products that contain the same active moiety or molecular structure. The same drug issue occurs when a sponsor applies for orphan drug designation for the same indication and the said drug has already been approved. In such cases, the sponsor must provide evidence that their medication is clinically superior to already approved products in terms of safety, efficacy, and quality.

Orphan Subset: "orphan subsets" fall under 21 CFR 316.3(b) (13); these are drugs used to treat

rare conditions that occur in 200,000 or more individuals and are still eligible to fall under the orphan drug designation, meaning the drug can be used in a subset of the population that does not have a rare disease, but the use of the drug outside of this subset should be monitored because of the composition of the drug. Orphan subsets are not commonly granted.

Ex- an orphan drug that uses antibody-specific targeted therapy is granted "orphan subset" designation since this specific antibody-targeted therapy can also be used in certain patients with non-rare diseases (distinct subtypes of tumors possessing that antigen).

Regulatory Status: the sponsor must make sure that complete information regarding investigational new drug application (IND) or new drug application (NDA) is submitted to the FDA; the regulatory status of the orphan drug in other countries can also be specified in your application, the sponsor must designate their product as a drug/biologic/device before submitting the application.

Population Estimate: the population estimate for an orphan disease is required to submit an orphan drug designation application; the population estimate for a condition is determined based on incidence or prevalence.

1. Prevalence is the number of people diagnosed with the rare disease at the time of submission of an orphan drug designation application.

2. Incidence is the annual number of cases reported for a disease or condition.

Orphan Drug Incentives and Market Growth: The U.S. was the first country to pass orphan drug legislation in the world; the main aim of this Act was to provide incentives to pharmaceutical organizations to promote research, growth, and development of orphan drugs for rare diseases [21].

These incentives led to an increase in the approval for orphan drugs since the enactment of the Act in 1983. From 1983 to 1989, FDA approved 42 orphan drugs and biologics in the U.S. (33 drugs and nine biologics) [22]. In a study conducted in 2008, it was found that 1,892 applications were made to FDA for orphan products, out of which market approval was granted to 326 products for different indications, with cancer being the top leading category for drug approval [23]. A report published in 2010, the study stated that the orphan drug market accounted for 51% of market growth in the U.S. and reached $47.8 billion by 2011. It further predicted that by 2014 the orphan drugs could be a $76.2 billion market. The orphan drug market is expected to reach $340 billion by 2027 [24, 25].

CONCLUSION: In conclusion, increasing awareness about rare diseases, and developing orphan drugs for said rare diseases are critical areas of focus for the U.S. Food and Drug Administration. These programs have increased the number of treatments available for rare diseases. The orphan drug policies and incentives have highly contributed to the development of the orphan drug market but, at the same time, have their limitations with the price of an orphan drug, treatment affordability, and market access. There are still some gaps in the policies that are to be fulfilled, the future of orphan drug market looks promising.

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