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Review Article

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Orphan Drugs Overview and Regulatory review procedure

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Abstract

To treat, prevent, or diagnose a rare condition (such as Huntington's disease, myoclonus disease, Tourette syndrome, etc.), a treatment or vaccination is known as an orphan drug. Although the definition of uncommon diseases differs between countries, most take disease incidence, severity, and the availability of alternative therapy choices into account. The laws and policies that each area or nation adopts determine the laws and policies that apply to a rare disease. ODA (Orphan Drug Act, 1983) has been effectively promoting R and D investments to create new pharmaceutical products for the treatment of rare illnesses for the past 40 years. It has been implemented in a number of nations throughout the world (including the USA, Australia, the European Union, Japan, and others). Incidences of certain diseases have been rising faster than the rate at which new medications are discovered and developed. Most notably, it has been emphasised that China and India, the two most populous nations, lack national laws for orphan drugs and rare illnesses, which might have serious detrimental effects for their patient populations with uncommon diseases.

Keywords: Orphan disease, Rare disease, Orphan drugs, Incentives, Marketing exclusivity

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1. Introduction

A pharmaceutical that has been given the orphan medication designation has been created expressly to treat a rare medical condition known as a "orphan disease." It might be characterised as medicines that address public health needs but are not produced by the pharmaceutical industry due to financial constraints. Pharmaceutical inventors are frequently deterred from creating medicines for relatively limited patient groups by the rising expense of medication research, strict restrictions, and minimal return on investment. Eighty percent of uncommon illnesses have genetic causes now known. Other uncommon illnesses are brought on by Allergies and bacterial or viral infections are brought on by degenerative and proliferative factors. (1)

An serious public health concern and a problem for the medical community are orphan medications. (2) For the successful treatment of people with uncommon disorders, modern society still lacks choices. One effect of this has been an increase in the financial burden of a patient with such diseases due to the need for public health protection. (3) Researchers now have a new method to study these orphan diseases, which are frequently more complicated than prevalent diseases thanks to scientific advancements. The good news is that when all of these uncommon diseases are considered, they can no longer be classified as rare. Approximately 7000 distinct rare illnesses and disorders exist, and new ones are constantly being found. According to reports, there are roughly 250 new uncommon cases reported year, but only 200–300 orphan cases may receive an appropriate therapy. The majority of illnesses have an unknown, bacterial, viral, or environmental origin. Genetic disease is the exception. (4) The majority of orphan illnesses have effective or curative treatments, are uncommon, difficult, and frequently chronic, progressive, debilitating, or even life-threatening. (5)

1.1 Evolution of Orphan Drug Act (ODA)

Particularly detrimental effects were caused by the restrictions that followed the FD and C Act and the 1962 Amendment for orphan pharmaceuticals. Only four medications were available to treat uncommon disorders in 1965, according to Asbury (1992), since orphan pharmaceuticals are focused on tiny populations and have smaller profits. Legislation dramatically raised the costs involved in developing new pharmaceuticals, which led pharmaceutical firms to concentrate on treatments that would maximise earnings and the likelihood that their R&D expenses would be recovered.Due to the concentration on lucrative

"blockbuster" therapies, which are defined as medications that are predicted to produce over $1 billion in sales annually, many people believed that uncommon diseases were "orphaned" or largely disregarded by pharmaceutical companies. These medications received the designation "orphan drug" as a result of its neglect. Orphan drug development eventually became a focus of public policy in the late 1970s and early 1980s because to the influence of non-governmental organisations like the National Organisation for Rare Disorders (NORD) and patient advocacy groups. The Bayh-Dole Act, put into effect by Congress in 1980 (PL No. 96-517, 1984), gave grantees of government-funded R&D the ability to patent and licence their work. This was followed by the Orphan Drug Act in 1983. (6)

1.2 The Orphan Drug Act (ODA) of 1983

The FDA has only authorised 58 orphan designations prior to the Orphan Drug Act (ODA) of 1983, with less than 10 in the ten years prior to the ODA's passage (Pharma, 2013). Following the ODA, existing medications that met the criteria had to be reapproved in order to be given commercial exclusivity and the Act's advantages. The basic objective of the ODA, which includes numerous components, is to lower costs and boost profits on orphan drug manufacture. Additionally, the ODA permits the FDA to approve orphan drug designations faster than other medications, lowering costs. the length of time. (7) A 50% tax credit on R&D expenses was established a permanent part of the Act by Congress in 1997. This credit is applied to the costs of clinical trials for medications that have been given formal orphan drug classification by the FDA. (6) The seven years of market exclusivity rights that pharmaceutical corporations can get for orphan drugs, which give them a monopoly over the sale of the drug for a certain indication, are the most contentious aspect of the ODA.

The statute has undergone multiple amendments by Congress since it was passed. Initially, orphan status was only given to pharmaceutical companies that could prove that developing an orphan medicine would be financially unviable and that the expenditures would not be recovered through US sales. As long as there was no "reasonable expectation" that US revenues would surpass development expenses, orphan medications might be lucrative through global sales. Due to the difficulty some biotech therapies faced in acquiring patents, orphan drug exclusivity was only granted to non-patentable medications.

However, the ODA's prohibition was removed in a 1985 modification. The majority of orphan goods could, in fact, receive patents; but, because of the protracted approval procedure, many of the patents became unnecessary when the product was unable to reach the market. Congress enacted a measure in 1990 to restrict market exclusivity, but George H. W. Bush vetoed the change. On June 12, 2013, the FDA most recently changed the ODA in order to "clarify, streamline, and improve the orphan drug designation process."(8)

1.3 "Orphan Drugs" - Denotation in Various regions

1.4 United States

According to American law, an orphan drug is any medication developed in conformity with the Orphan Drug Act of January 1983 (ODA). Orphan illnesses are those that are either uncommon (fewer than 200,000 Americans are affected by them) or have a low prevalence (less than 5 per 10,000 people in the general population), and are governed by a federal statute known as the Orphan Drug Act (ODA). (9)

1.5 Europe

According to the Orphan Drug Regulation 141/2000, an illness is deemed uncommon in Europe if it affects fewer than 5 persons per 10,000. At first glance, this may seem like a minor number, but according to this definition, the number of persons in the European Union who have rare diseases might reach up to 30 million. There are between 6,000 and 8,000 uncommon diseases, the majority of which have genetic origins, according to EURORDIS (European Organisation for uncommon Diseases), and five new rare diseases are described in the medical literature each week. According to estimates, 25–30 million people in Europe are affected by these ailments. (9)

1.6 Japan

The three criteria stated below must be met for a medicine to be eligible for orphan drug designation in Japan. If there are less than 50,000 prevalent instances (0.4%) of a disease, Japan considers it to be rare. The proposed drug either treats an illness or condition for which there are no alternative therapies available in Japan, or it is clinically superior to drugs presently available on the Japanese market.

A clear product development strategy and supporting data from science are required by Japan for the application. A New Drug Application (NDA) may be submitted once clinical investigations are finished. Although there are rules in Japan that regulate orphan medications, it's important to keep in mind that these laws are open to interpretation. (9)

1.7 Australia

The Therapeutic Substances Regulations only states that whether it is a vaccination or in-vivo diagnostic, it must not be intended for use in more than 2000 patients annually. It does not define a rare illness or orphan indication addressing the number of patients. The "application must show why the medicine is an orphan drug" in order to receive the classification of orphan drug. medications used to treat illnesses or ailments that afflict fewer than 2,000 people at a time are known as orphan medications in Australia (0.2%). (9)

1.8 India

The proposal by the Indian Pharmacists and the Government to enact Laws, which would build the health infrastructure and bring relief to the countless rare illness patients throughout the country, makes it clear that such an act is necessary. In 2001, the Drugs Manufacturers Association asked the Indian Government to implement the Indian Orphan Drug Act. (9)

2. Review Process for Orphan Drugs in Various Countries

2.1 US

The FDA's top goal is assisting in the development and assessment of novel therapies for rare illnesses. A medicine or biological product can be given the orphan drug designation by the FDA if it is intended to prevent, identify, or treat a rare illness or condition. When a medicine is designated as an orphan, sponsors may be eligible for rewards like:

- For eligible clinical trials, tax credits.
- a waiver of user fees.
- After authorised, there might be a seven-year commercial exclusivity period.

The government must receive a request for designation from sponsors who want their medicine to be designated as an orphan drug. Sponsors must provide their own statistics and material to support their designation request if they want to designate the same medication for the same uncommon disease or condition as a product that has already been designated. The designation of an orphan medication is a distinct procedure from applying for approval or licencing. Drugs for rare illnesses must pass the same exacting scientific review procedures as regular medicines before they can be approved or licenced. (10)

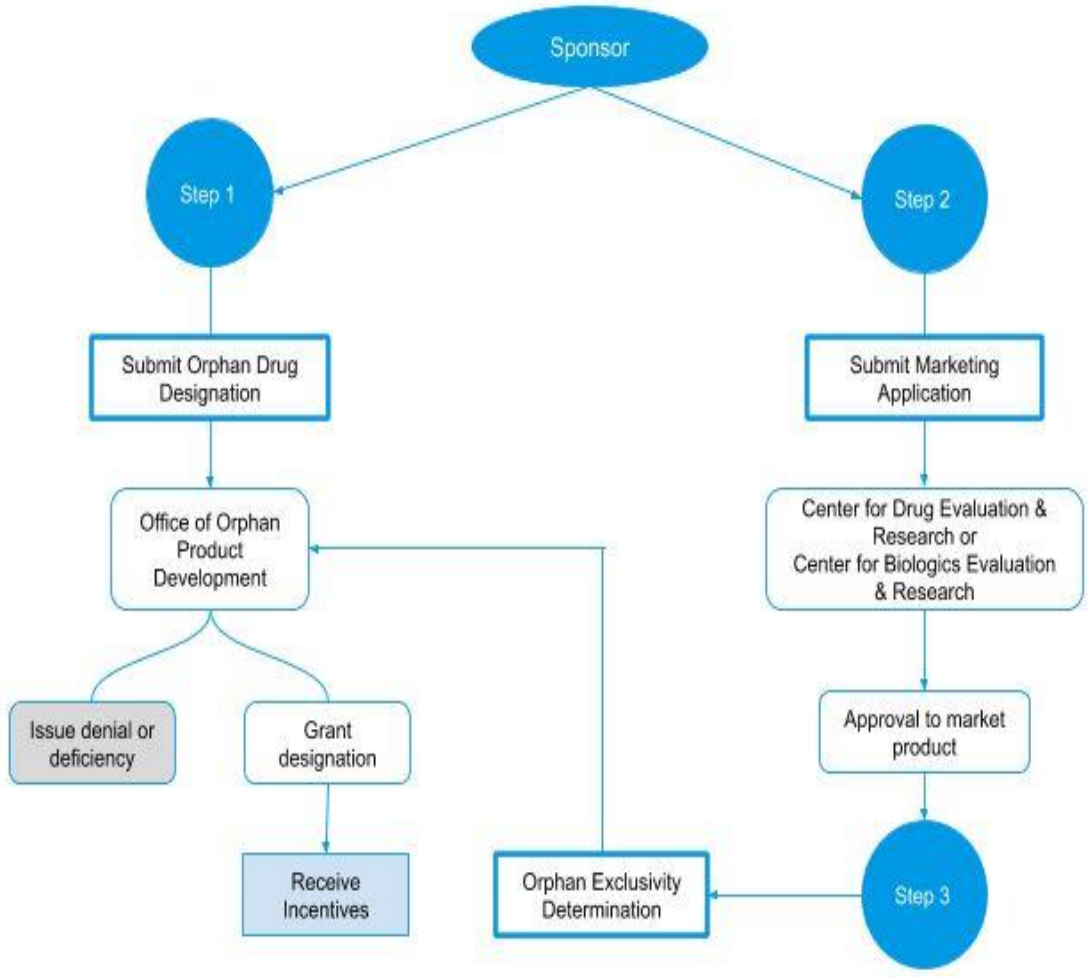

Figure 1. Review Process for Orphan Drugs in US (11)

2.2 European Union

Applications from sponsors for orphan designation must be reviewed by the Agency. A medication must fulfil a number of requirements in order to be designated as an orphan drug:

the condition must not affect more than 5 out of 10,000 people in the EU, or it must be unlikely that marketing the drug would bring in enough revenue to cover the costs incurred in its development; it must be intended for the treatment, prevention, or diagnosis of a life-threatening or chronically debilitating disease.

No adequate technique of the ailment's diagnosis, prevention, or treatment may be approved, or if one does, the drug must significantly benefit persons who are affected by the illness.

The Committee for Orphan Medicinal Products (COMP) of the European Medicines Agency (EMA) reviews requests for orphan designation utilising its network of specialists. After validation, the assessment procedure takes up to 90 days. The Agency notifies the European Commission, which is in charge of awarding the orphan status, of the COMP opinion. (12)

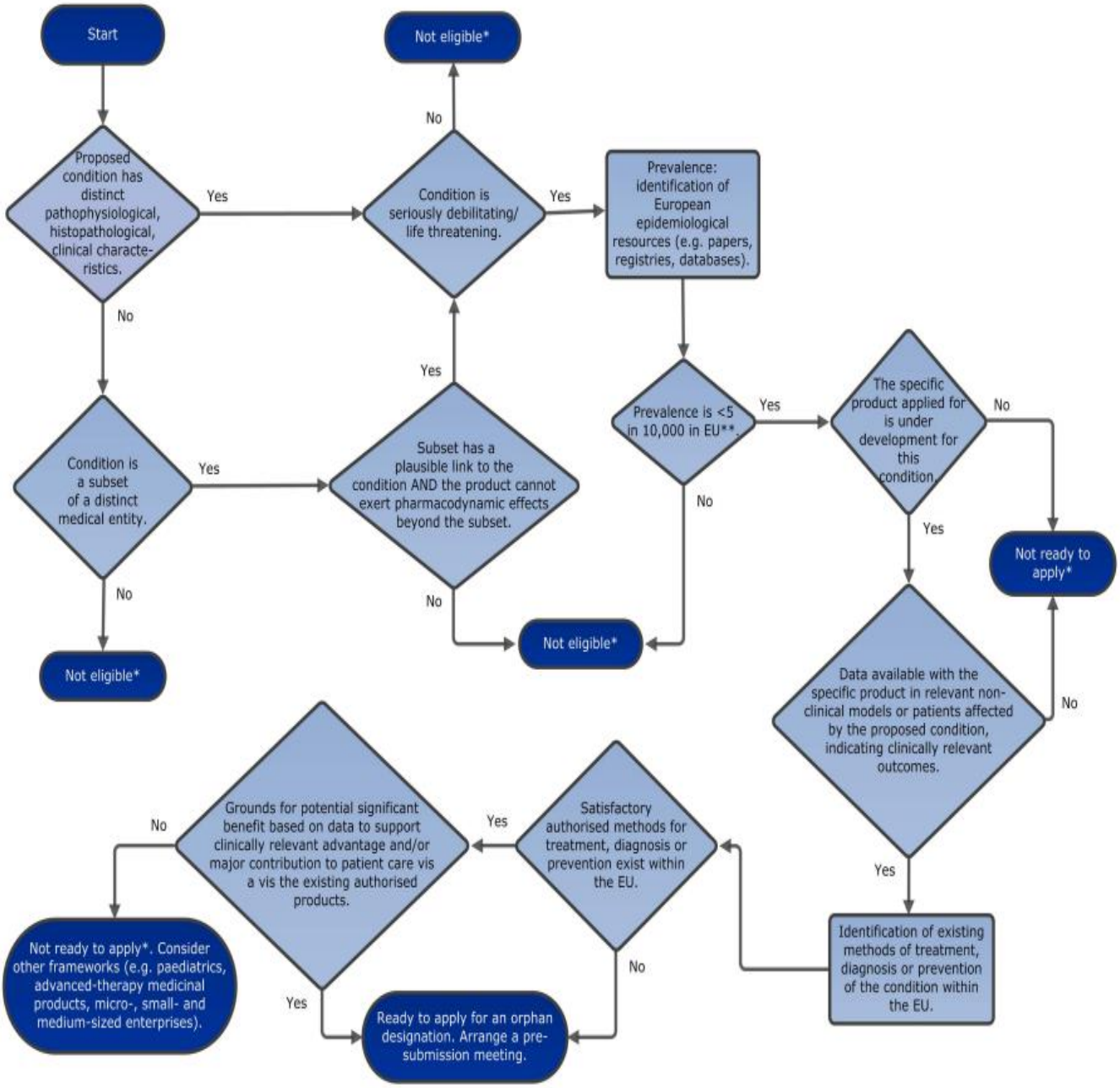

Figure 2. Review Process for Orphan Drugs in European Union (13)

2.3 Japan

Applications for orphan drug/medical device designation can be submitted at any time. After the receipt of application, the designation will be determined based on the discussion at Pharmaceutical Affairs and Food Sanitation Council (PAFSC).

- MHLW- Ministry of Health, Labour, and Welfare
- PMDA- Pharmaceuticals and Medical Devices Agency
- NIBIO- National Institute of Biomedical Innovation
- PFSB- Pharmaceutical and Food Safety Bureau
- PAFSC- Pharmaceutical Affairs and Food Sanitation Council (14)

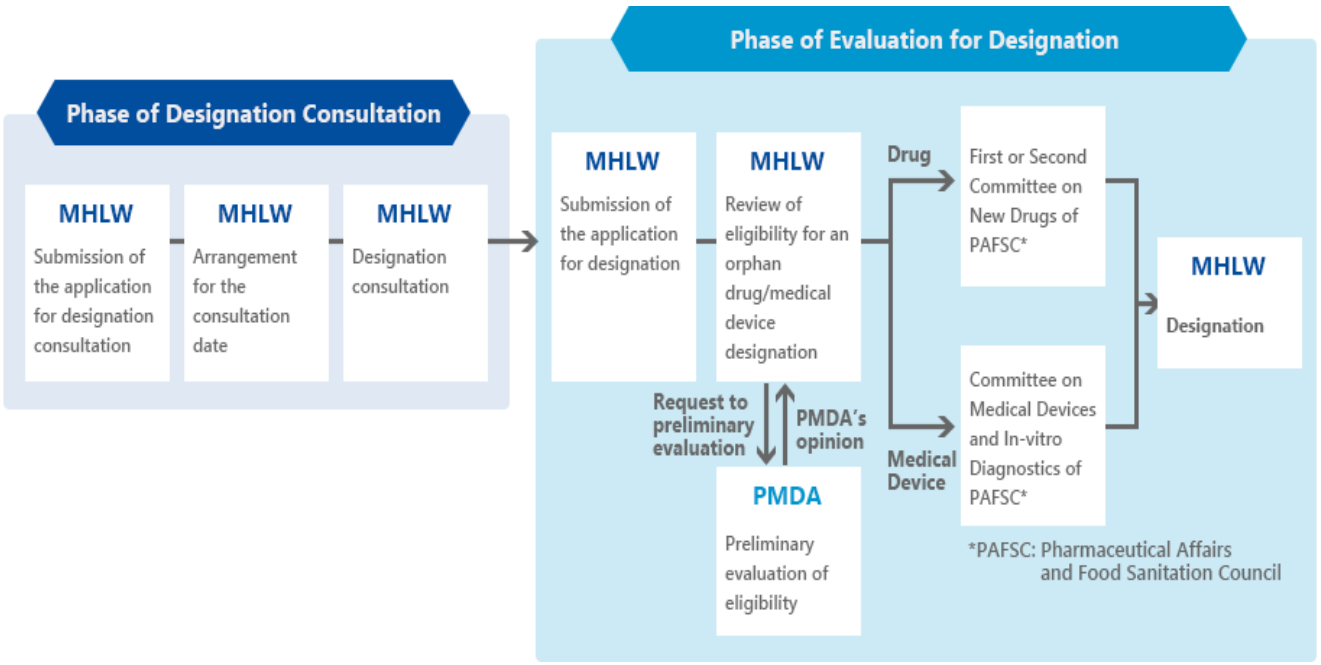

Figure 3. Review Process for Orphan Drugs in Japan (15)

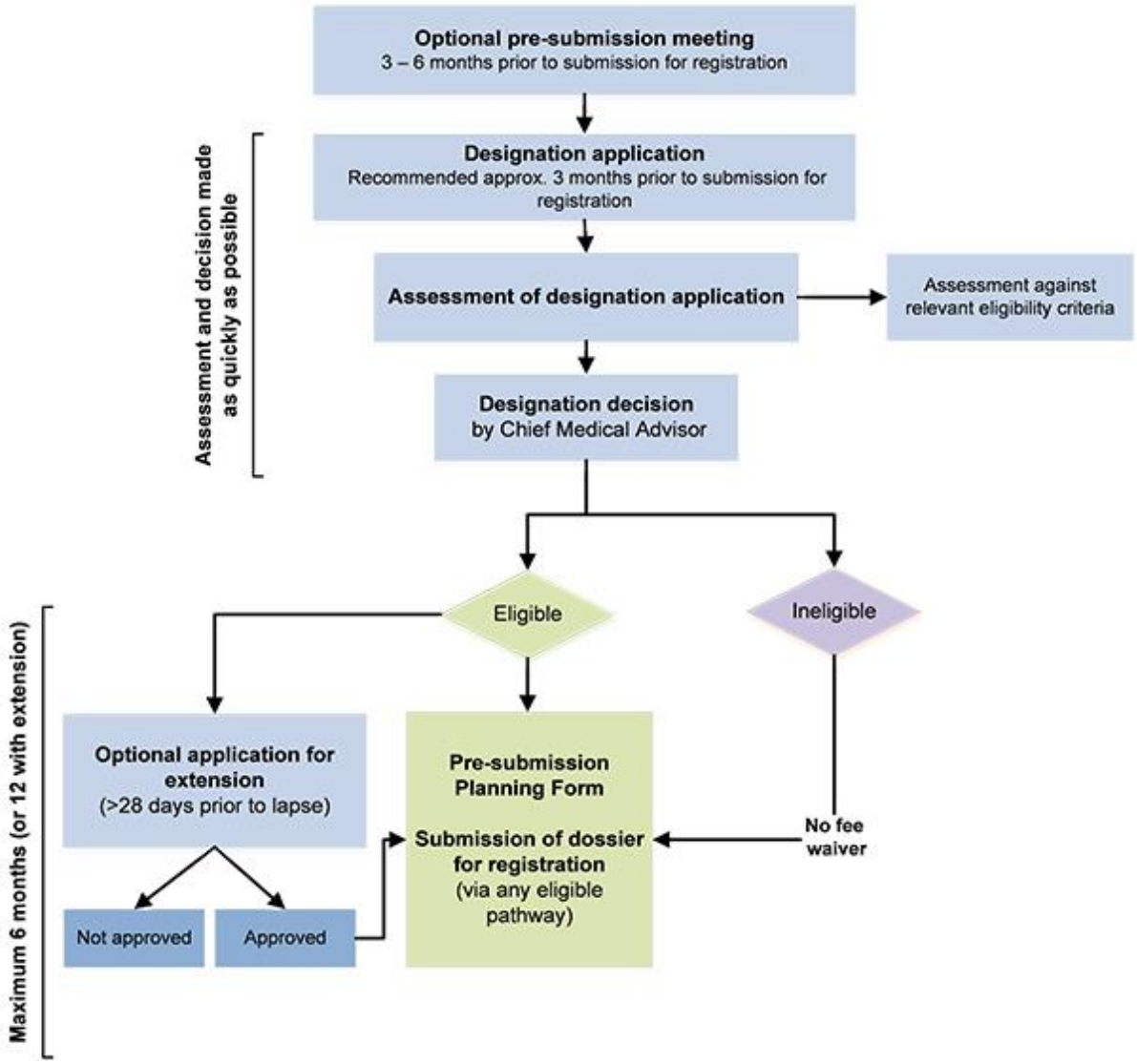

Figure 4. Review Process for Orphan Drugs in Australia (16)

2.4. Australia

Designation is a formal process that allows us to make a decision under regulation 16J of the *Therapeutic Goods Regulations 1990* (the Regulations) regarding whether the medicine is eligible for orphan drug designation. The *designation application* precedes the registration application and is the formal application made using a specified form requesting assessment against the relevant eligibility criteria and a decision from TGA. Application and evaluation fees are waived for prescription medicine registration applications if a related orphan designation is in force. (17)

3 Incentives

Orphan medications are available and accessible thanks to both financial and non-financial incentives. Below, we list these:

a. Economic incentives (financial incentives).

b. Nonmonetary Incentive (non-financial incentives).

a. Economic incentives.

Research grants, tax credits and corporate tax reductions, commercial exclusivity, and fee waivers are only a few of the financial inducements used globally. Due to the tiny market sizes for orphan medications, these rules exist to provide businesses a way to recoup their research and development expenditures. (18)

The availability of orphan pharmaceuticals is often aided by these financial incentives; according to research by Blankart et al., only 10% of clinical studies for orphan drugs would have been done without them. (19)

b. Nonmonetary Incentive

Fast track clearance, pre-licensing access (in the form of compassionate or off-label access), and scientific guidance, which includes free protocol help and development consultation, are some of the non-financial incentives that we discovered. Four nations—France, Italy, Spain, and the Netherlands—allow pre-licensing access to orphan pharmaceuticals but promote the gathering of further clinical data to demonstrate a therapeutic effect, according to research by Garau et al. (20)

Pre-licensing permits the importation of orphan pharmaceuticals that are legal in other nations but are now illegal in the United States. In many nations, pre-licensing access—often through practises like named patient procedures—is the most popular way for patients to get orphan medications. An individual or group of patients with a significant or persistent condition may be given permission to utilise this a fatal condition for which there is no effective alternative treatment. (21)

Regulatory agencies offer free scientific guidance, including protocol support, to improve clinical trials and research procedures and raise the possibility of a successful marketing authorisation and subsequent reimbursement application. (22)

4. Marketing Exclusivity

When it comes to vaccinations, diagnostics, and preventative medications that are intended to treat disorders that affect a very small number of individuals or for which there is no realistic hope that the expenses of research and development would be recouped, the term "orphan drug exclusivity" is used. (13) The sponsor's information is used to determine whether to approve an application for orphan designation. "Orphan status" refers to a medication that has received orphan classification. (24) The "standard regulatory requirements and process for obtaining market approval" must be followed by sponsors. (25) For a medicine that has already been commercialised or was previously disapproved, a sponsor may ask for orphan drug classification. For the same medication used to treat the same uncommon disease or condition, more than one sponsor may be granted orphan drug classification. A medicine that has been designated as orphan is given exclusive approval and sales exclusivity. (6)

Table 1. Orphan Drugs: Market Overview and Country- Specific Analysis

Parameters	USA	EU	Japan	Australia
Regulatory authority	United State Food & Drug Administration (USFDA)	European Medicines Agency (EMA)	Pharmaceuticals and Medical Devices Agency (PMDA)	Therapeutic Goods Administration (TGA)
Regulatory authority Website	https://www.fda.gov/	https://www.ema.europa.eu/en	https://www.pmda.go.jp/english/	https://www.tga.gov.au/
Regulatory authority Flag				
Legal framework	Orphan Drug Act (1983)	Regulation (CE) N°141/2000 (2000)	Orphan Drug Regulation (1993)	Orphan Drug Policy (1998)
Administrative authorities involved	FDA /OOPD	EMEA/COMP	MHLW/OPSR (Orphan Drug Division)	TGA
Prevalence of the disease (per 10,000 individuals), justifying the orphan	7.5	5	4	1.1

status				
Estimation of the population affected, prevalence rate (per 10,000 individuals)	20 millions	25–30 millions	No information	No information
Marketing exclusivity	7 years	10 years	10 years	5 years (similar to other drugs)
Tax credit	Yes: 50% for clinical studies	Managed by the member states	Yes: 6% for any type of study + limited to 10% of the company's corporation tax	No
Grants for research	Programs of NIH and others	"FP6" + national measures	Governmental funds	No
Reconsideration of applications for orphan designation	No	Yes (every 6 years)	Yes	Yes (every 12 months)
Technical assistance for elaboration of the application file	Yes	Yes	Yes	No
Accelerated marketing procedure	Yes	Yes (via the centralized procedure)	Yes	Yes

5. Conclusion:

Only in a few nations have orphan medication programmes for uncommon illnesses been successful. Finding the ideal incentive structure might be challenging in markets with little first-mover advantages. Orphan products are now being developed, approved, and more readily available because to the ODA's approach. Although the market exclusivity clause has increased access to orphan treatments, it could be mistakenly giving other items exclusive market protection.Depending on the amount invested in research and development, the return on that investment, the tax and patent incentives, and the regulatory laws of the nation, significant pharmaceuticals should be produced for the benefit of the entire globe. If these things are agreed upon, our country's mentality may change for the better and help avoid "orphanisation of new drugs."

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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