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COMPREHENSIVE REVIEW ON ORPHAN DRUG REGULATIONS IN THE USA, EU, JAPAN, AND AUSTRALIA: POSSIBLE RECOMMENDATIONS TO SPECIFIC CHALLENGES

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ABSTRACT: Orphan drugs are medicinal products intended to diagnose, prevent, or treat life-threatening or debilitating rare diseases. In some parts of the world, a rare disease is also addressed as an orphan disease due to its poor diagnosis mechanism, low prevalence, and limited treatment options. The United States, Japan, Australia, and the European Union have adopted policies promoting orphan drugs development and commercialization. The United States was the first nation to adopt a law on orphan drugs in 1983, followed by Japan (1993), Australia (1998), and the European Union (2000). Orphan drug development also possesses challenges like limited scientific knowledge, low number of patients available, high pricing of these drugs & other regulatory challenges. This review compared the orphan drug regulations in the USA, the EU, Japan, and Australia and addressed the challenges involved in orphan drug development along with possible recommendations.

INTRODUCTION: World health organization defined Rare Disease as a disease or condition with a prevalence of less than one person per 1000 population. However, different countries have their own definitions to suit their specific requirements and in the context of their own population, health care systems, and resources [1]. Some definitions rely solely on the number of people living with a disease, and other definitions include factors such as the existence of adequate treatments or the severity of the disease. In certain parts of the world, rare diseases are also addressed as orphan diseases due to their poor diagnosis mechanism, low prevalence, and limited treatment options.

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A disease can be rare in one area; however, common in another. This is the case of 'thalassemia, an anemic of genetic origin, rare in Northern Europe, but it is common in the Mediterranean region. To date, 6,000 to 7,000 rare diseases have been discovered. Most rare diseases are genetic and thus present throughout the person's entire life. There are also sporadic forms of infectious diseases, such as auto-immune diseases and rare cancers. Rare diseases are severe, often chronic, and progressive diseases [2].

The rising case of rare diseases has encouraged the key players to develop new and advanced treatments, projected to drive the market in the next few years. The global orphan drug market is predicted to attain a net valuation of US$318.5bn by the end of 2025 [3]. Different countries were done to regulate orphan drugs and introduce a set of commercial incentives to stimulate the production of orphan drug products. The United States was the first country to adopt an orphan drug act in 1983,

followed by several other countries, such as Japan (1993), Singapore, Australia (1998), and the EU (2000). In Europe, Union acts were done much later than the USA because it is a group of 28 countries, and its capabilities regarding health are very much dispersed. The incentives offered to orphan drug developers and manufacturers have contributed to increased research in this area.

2. Orphan Drug Regulations in the USA: The US Orphan Drugs Act (ODA), amending the US Federal Food, Drug and Cosmetic Act, was enacted on 4 January 1983. The Act was administered by the FDA OOPD (Office of Orphan Products Development). The Orphan Drug Act offers incentives to encourage the development of promising medicines and biologics to prevent, diagnose, or treat rare diseases.

According to US Orphan Drugs Act, the term rare disease means any disease or condition which:

(a) Affects less than 2,00,000 persons in the US or (b) Affects more than 2,00,000 persons in the US, but for which there is no realistic assumption that the cost of developing and availability of medication for such a disease or condition in the US would be recovered from sales of such a drug in the US [4]. For a drug to qualify for orphan designation, both the drug and the disease condition must meet the criteria specified in the ODA and FDA's implementing regulations at 21 CFR Part 316. The safety and efficacy of a drug must be established through adequate and well-controlled studies [5]. The FDA form 4035 is designed to assist sponsors in providing the required content for orphan designation [6].

2.1 Orphan Drug Status: Orphan Drug Status is given to a drug if it meets the following criteria:

a. A drug that is not approved earlier.
b. An approved drug with a new orphan indication.
c. A drug proved clinically superior over a previously approved drug of the same category [7].

2.2. Orphan Designation Application Content: To designate as an orphan drug product, the sponsor must submit the information to the OOPD. The documentation for developing a product is rational for use in a specific disease and has a reasonable scientific basis and prevalence criteria of fewer than 2,00,000 patients in the USA [4].

A summary of the pre-clinical and clinical data of the concerned product and essential documentation should be provided. Clinical trial data is preferred, but the scientific rationale can be sufficiently backed by 'compelling' pre-clinical data in the relevant animal model in the absence of data. The application must include prevalence criteria and a scientific rationale that establishes a plausible medical hypothesis. As outlined in *21* CFR *316.3*(b)(*14*), if the sponsor is applying for the same drug already approved, the sponsor must include information on the plausible hypothesis for clinical superiority on efficacy or safety or significant contribution to the patient care. If the product is claimed to be non-profitable for seven years after its marketing approval, an assessment of the costs of drug production and distribution, and an estimation of potential sales in the United States, shall be made to confirm, in particular, the lack of economic viability of drug marketing [4,7]. The content and format for orphan drug designation are described in *21* CFR *316.20*. The content of the designation application in the USA is given in **Table 1**.

TABLE 1: LIST OF DOCUMENTS INCLUDED IN THE ORPHAN DESIGNATION APPLICATION IN THE USA [8]

S. no.	Basic elements	Description
1	Administrative information	Descriptive name of the product Manufacturer for drug substance/drug product.
2	Explaining what is the disease or condition	Mechanism of action of drug pathophysiology, Etiology, Treatment options, Prognosis
3	Providing sufficient scientific rationale	Drug description and MOA relevant to disease/condition. *in vitro*, *in vivo*, clinical studies data relevant to drug and disease/condition
4	Determining the population estimate to support that the disease is rare	Foreign, geographically restricted, or old data Registries, databases, literature searches Estimate must be current as of the time of application submission All calculations and references used to derive the population estimate

2.3. Orphan Drug Designation Procedure in the USA: The sponsor may apply to the OOPD at any time before the submission of the marketing authorization application [9]. An online portal for submission of Orphan drug designation requests was recently launched in November 2020 [5]. A foreign sponsor must hire a US resident agent to file an orphan drug designation application [7]. Upon receiving the orphan drug designation request at OOPD, the request is assigned a designation request number, logged into the OOPD database, and an acknowledgment letter is sent to the sponsor. The scientific staff of the OOPD reviews a submitted orphan drug application to assess whether a drug qualifies as an orphan medicinal product. The assigned OOPD reviewer shall complete the submission review, which may include consultation with the FDA center. The review is then forwarded to the Orphan Drug Designation Program Director for a second-level review and concurrence [10]. A letter of designation, a letter requesting additional information, or a rejection letter is the outcome. Following a favorable decision, the sponsors' name, name of the drug and proposed indications are published. The typical review cycle is 90 days [11]. The Orphan designation procedure in the USA is shown in **Fig. 1**.

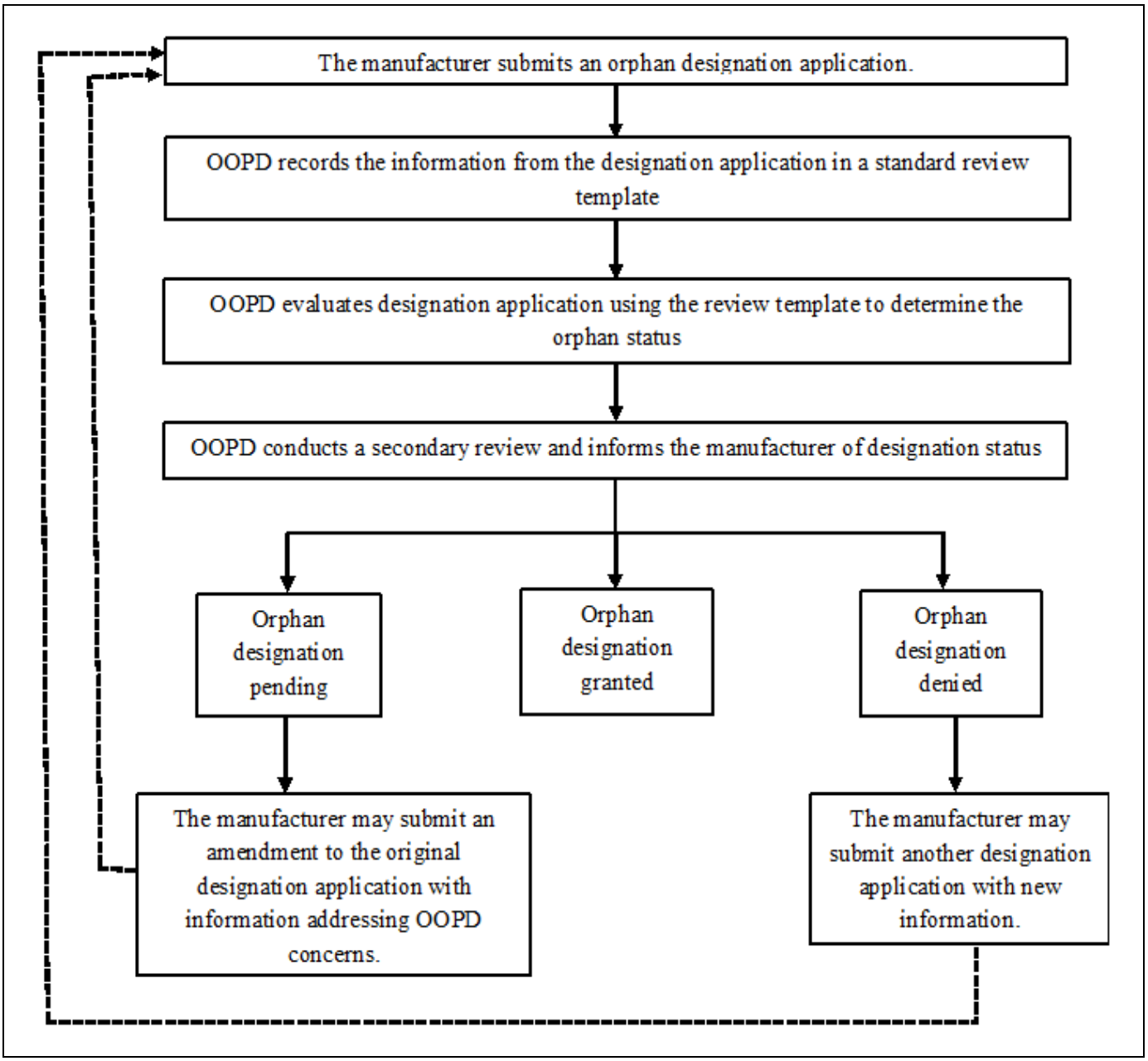

FIG. 1: ORPHAN DESIGNATION PROCEDURE IN THE USA

2.4. Incentives provided by the Orphan Drug Act: The following incentives are applied to the products after the orphan designation is granted.

1. Protocol assistance: Giving scientific advice to the developers of designated orphan medicines for rare diseases.
2. Reduced/waived regulatory fees: Giving some exemptions, *i.e.,* reduces fees while filing NDA for orphan drugs under PDUFA.
3. Tax credit on clinical trials: The orphan drug tax credit gives a credit of 50% of the clinical testing costs for the development of drugs.
4. Specific subsidies for clinical trials: The Orphan Products Grants Program provides funding for clinical trials to advance the rare disease research and development of orphan drugs.
5. Seven years of marketing exclusivity: Seven years of marketing exclusivity is granted from the date of marketing approval of a drug. During this period, no other sponsor may obtain the same drug's approval for the same use except under limited circumstances. However, the FDA may approve a different drug for the same indication [7, 12].

2.5. Activities after Orphan Designation: An orphan designation sponsor is obligated to submit an annual report within 14 months after the date on which the orphan drug designation was granted and annually until marketing approval. The annual report should contain:

- **a.** The progress of drug development, including a review of pre-clinical and clinical studies initiated.
- **b.** A description of the investigational plan for the coming year, as well as any anticipated difficulties in development, testing, and marketing; and
- **c.** A brief discussion of any changes that may affect the product's orphan-drug status [13].

2.6. FDA's Marketing Approval Process: Granting an orphan designation request does not alter the standard regulatory requirements for obtaining marketing approval in the US. To market a new drug, the applicant has to submit NDA or BLA to FDA, regardless of orphan drug status.

Since, orphan medicines are mostly developed to treat patients with unmet medical needs, they may receive one or more expedited FDA programs. FDA's four expedited programs are accelerated approval, breakthrough therapy designation, fast track designation, and priority review. These programs are intended to facilitate and expedite the development and review of new drugs to address unmet medical needs in treating a severe disease [7, 9].

3. Orphan Drug Regulations in Europe:

3.1 Regulation (EC) No 141/2000: This regulation establishes a community procedure for the designation of medicinal products as orphan medicinal products and provides incentives for the research, development, and marketing of designated orphan medicinal products. This regulation also establishes the Committee for Orphan Medicinal Products (COMP) [14].

3.1.1 Criteria for Designation: Article 3 of EC No 141/2000 defines; a medicinal product shall be designated as an orphan medicinal product if its sponsor can establish:

a) That it is intended for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition affecting fewer than 5 in 10 thousand persons in the Community, or that it is intended for the diagnosis, prevention, or treatment of a life-threatening, seriously debilitating or severe and chronic condition in the Community and without incentives, it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment.

b) That there is no satisfactory method of diagnosis, prevention, or treatment of the condition in question has been authorized in the Community or, if such a method exists, the medicinal product should provide significant benefit to those affected by that condition [14].

3.1.2. Incentives:

1. Scientific advice and consultation during the development phase of orphan drugs.
2. Complete reduction for protocol assistance fee and follow-up fee.
3. Complete waiver of fees for pre-authorization inspections, 50% decrease in the new applications for marketing approval to large-sized enterprises, a complete waiver for marketing authorization, and post-approval endeavours in the first year, only to small and medium-sized enterprises.
4. Ten years of exclusive marketing. However, this period may be reduced to six years if, at the end of the fifth year, that the criteria laid down in Article 3 are no longer met [14].

3.2. Commission Regulation (EC) No 847/2000: This regulation lays down factors to be considered when implementing Article *3* of Regulation (EC) No 141/2000 on orphan medicinal products and establishes definitions of 'similar medicinal product' and 'clinical superiority.' It is intended to assist sponsors, the Committee for Orphan Medicinal Products, and the competent authority [15].

3.2.1. Prevalence of a Condition in the Community: If the applications are based on the low prevalence and incidence rate as outlined inarticle 3(1)(a) of Regulation (EC) No 141/2000, the documentation listed below:

a. The documentation shall include authoritative references that demonstrate the prevalence criteria of a disease or condition not more than 5 in 10,000 persons in the Community.

b. The data shall include appropriate justification of the condition's life-threatening or chronically debilitating nature supported by scientific or medical references.

c. The documentation shall include reviewing the relevant scientific literature and shall provide information from relevant databases in the Community.

Where no database within the Community is accessible, reference may be extrapolated to databases available in third countries [15].

3.2.2. Potential for Return on Investment: If the applications are based on the insufficient return of the investment as outlined in article 3(1)(a) of Regulation (EC) No 141/ 2000, the documentation shall include:

a. Appropriate justification of the life-threatening or seriously debilitating nature of the condition is supported by scientific or medical references.

b. Data on all costs incurred by the sponsor in developing the medicinal product and a justification of all expenses for the development and production anticipated by the sponsor after applying for designation.

c. Details of any grants, tax incentives, or other cost recovery provisions received within the Community or third countries.

d. Information on the prevalence and incidence of the condition in the Community [15].

3.2.3. Existence of Other Methods of Diagnosis, Prevention, or Treatment: According to Article 3(1)(b) of Regulation (EC) No 141/2000 that there exists no satisfactory method of diagnosis, prevention, or treatment of the condition in question, or if such method exists that the medicinal product will be of significant benefit to those affected by that condition, the following rules shall apply:

a. Details of any current diagnosis, prevention, or treatment methods of the condition that have been authorized in the Community shall be provided, referring to any scientific and medical literature.

b. A rationale for the presumption that those affected by the condition would benefit substantially from the medicinal product[15].

As outlined in article *3* of Regulation (EC) No 847/2000, 'Similar Product' and 'Clinical Superiority' are defined as follows:

Similar Product: If the active substance is considered similar in its molecular structural features, the mechanism of action, and the therapeutic indication.

Clinical Superiority: There exists no satisfactory method of diagnosis, prevention or treatment of the condition in question, or if such method exists that the medicinal product will be of significant benefit to those affected by that condition" [15].

3.3. Commission Regulation (EC) No 726/2004: On 31 March 2004, the European Parliament adopted Regulation (EC) No 726/2004, which provides the legal framework for the centralized authorization and supervision of medicines for human and veterinary use. According to this regulation, all marketing authorizations for orphan medicines in the EU should follow the centralized authorization procedure. The CHMP is also authorized to issue guidance regarding compassionate-use programs [16].

3.4. Commission Regulation (EC) No 507/2006: On 29 March 2006, the European Parliament adopted Regulation (EC) No 507/2006. It establishes that orphan medicines can be granted conditional marketing authorization to medicines that fall within the scope of Regulation (EC) No 726/200417.

3.5. Commission Regulation (EC) No 1901/2006: On 12 December 2006, the European Parliament adopted Regulation (EC) No 1901/2006 on medicinal products for paediatric use. It establishes that the usual period of market exclusivity for orphan medicines may be extended to 12 years if study results are submitted in compliance with an agreed pediatric investigation plan [18].

3.6. Applying for Orphan Designation: A sponsor applying for an orphan medicinal product designation shall apply at any stage of the development, but usually before submitting the marketing authorization application (MAA). Where possible, sponsors should notify the European Medicines Agency (EMA) of their intention to submit an application at least two months before the planned submission date. A sponsor may apply the designation for an already approved medicinal product of an unapproved therapeutic indication. More than one sponsor may apply for designation as an orphan medicinal product for the same medicinal product intended to diagnose, prevent, or treat the same or a different condition [19]. Sponsors need to use EMA's secure online IRIS platform to submit orphan designation applications and manage pre-and post-designation activities [20]. Applications must be submitted to EMA in conformity with the procedural guidance on the content and format of orphan drug designation applications.

The content of the designation application in the EU is given in **Table 2**.

TABLE 2: LIST OF DOCUMENTS INCLUDED IN THE ORPHAN DESIGNATION APPLICATION IN EU [21]

S. no.	List of documents	Description	Format
1	Application form	Administrative information Sponsor information Corresponding contact person OD number	Webform in EMA‟s online system IRIS.
2	Scientific document: Section A to E	Description of the condition Prevalence of the condition Potential for return on investment Description of the stage of development Other methods for diagnosis, prevention/ treatment of the condition.	Word/RTF format.
3	Proof of establishment of the sponsor in the EU	If the sponsor is an organization should have a permanent physical address in one of the countries of the EEA and provide full details in the application form, including the name of a contact person. If the sponsor is a natural person of a country of the EEA, they should not include proof of establishment in the portal folder of the submission to respect data protection rights and freedoms.	PDF
4	Translations	Product name and proposed orphan indication, translated into all official languages of the European Union, incl. Norwegian and Icelandic.	Word
5	References	Scientific articles are cited throughout the application as single PDF files	PDF (Zip file)

3.7. Orphan Drug Designation Procedure in EU: Once the designation application is submitted following EMA's submission schedule, the application will be validated and evaluated by EMA's designated scientific administrator and one member from the COMP.

Day 1 - A summary report will be prepared and forwarded to all COMP members for review and consequently discussed at the next meeting (day *60*).

Day 60 - The COMP will either issue a list of questions to the sponsor for the response or adopts a positive opinion, which will be forwarded to the EC for adoption.

Day 90 - The EC issues a decision within 30 days of receipt of the COMP's opinion (i.e., on day *90)*. EMA will publish the information at the Community register of designated orphan medicinal products.

If the outcome of the review process is negative, COMP notifies the sponsor regarding the issuance of a negative opinion. The sponsor may withdraw the designation application and should inform EMA in writing before the negative opinion is issued. The sponsor can resubmit the orphan designation with revised or additional data anytime thereafter.

Detailed reasons for appeal must be submitted within 90 days based on the new supporting data. This data will be distributed to all members of the COMP and will be addressed again at the next plenary session.

A positive or negative opinion will be issued at this stage, a summary of the opinion published on EMA's web page, and a European Commission decision adopted [22].

The Orphan designation procedure in the EU is shown in **Fig. 2**.

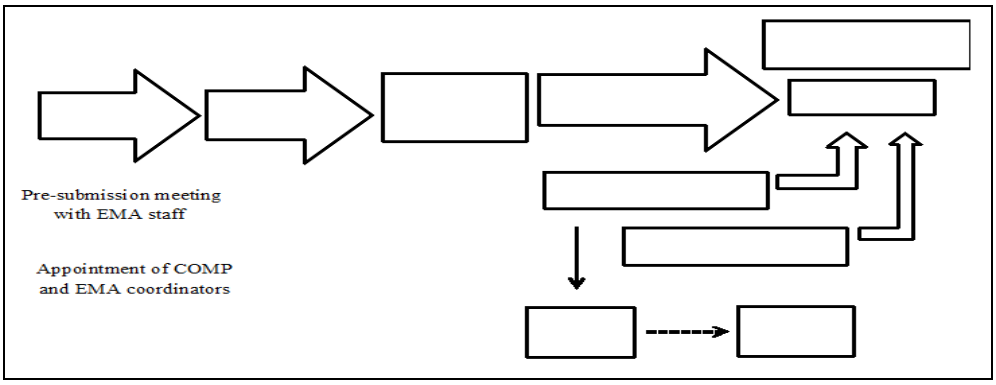

FIG. 2: ORPHAN DESIGNATION PROCEDURE IN EU

3.8. Activities after Orphan Designation: According to article 5(10) of Regulation (EC), No 141/2000, the sponsor of an orphan drug designation is obligated to submit an annual report on the state of development of designated medicinal products to the EMA. The annual report should contain a review of ongoing clinical studies, a description of the investigation plan for the coming year, any anticipated or current problems in the process, difficulties in testing, and potential changes that may impact the medicine's orphan designation. Annual reports must be submitted within two months following the anniversary of the approved designation. These reports must be prepared and submitted to the EMA annually until the first application for marketing authorization is submitted in the EU [23].

3.9. Activities during Marketing Authorization Application: According to Article 3(1) of Regulation (EC) No 726/2004 for orphan medicinal products, a centralized process is required to apply for marketing authorization. The sponsor is obligated to submit a report on maintenance of the orphan designation and marketing authorization application around day 121 of the standard MA procedure (210 days). Market exclusivity is linked to the maintenance of the orphan designation when the medicine receives marketing authorization for the indication concerned. The COMP reviews the maintenance of orphan designation based on the data available and the sponsor's report and issues an orphan maintenance assessment report. The COMP adopts an opinion on the orphan designation review following the CHMP positive opinion on the

marketing authorization application. EMA sends the COMP opinion to the European Commission.According to Article 8(3) of the Orphan Regulation (EC) No 141/1200, if the medicinal product under evaluation is considered as similar to an authorized orphan product, a marketing authorization will not be granted unless the sponsor can demonstrate that the medicinal product is significantly safer or clinically superior [24].

4. Orphan Drug Regulations in Japan: In June 1985, the Pharmaceutical Affairs Bureau of the Japanese Ministry of Health and Welfare (MHW) issued a notification on orphan drug development. This notification allowed the applicant to submit a simplified Japanese new drug application (J-NDA) for orphan drugs [25].

4.1. Japan Pharmaceutical Affairs Law (revised in 1993): In 1993, Japan revised its Pharmaceutical Affairs Law intended to include essential measures that support pharmaceutical companies to develop orphan medicinal products [26].

In Japan, drugs and medical devices are designated as orphan drugs or medical devices based on Article 77-2 of the Act on safeguarding the Quality, Efficacy, and Safety if they are intended for use in fewer than 50,000 patients in Japan and for which there is a high medical requirement.

Based on the opinion of the Pharmaceutical Affairs and Food Sanitation Council (PAFSC), the designations are approved by the Minister of Health, Labour, and Welfare (MHLW) [27].

4.2. Organization of the Orphan Drug Designation System: The functions of regulatory authorities involved in the designation system are listed below.

I. Ministry of Health, Labour and Welfare (MHLW):

- **a.** Review and approval of designation and registration of orphan drugs/medical devices.
- **b.** Allows Pre-designation consultation for orphan drugs/medical devices.
- **c.** Supports Payment for the operational cost of NIBIO.

II. Pharmaceuticals and Medical Devices Agency (PMDA): PMDA provides priority scientific consultation for clinical trials and dossiers for marketing authorization of orphan drugs/medical devices.

III. National Institute of Biomedical Innovation (NIBIO): It provides:

- **a.** Subsidy payment to the applicant.
- **b.** Accreditation for research expenses to be used by the applicant.
- **c.** Provision of guidance and consultation to the applicant [27].

4.3. Eligibility Criteria for Orphan Drug Designation in Japan: The Minister of Health, Labour, and Welfare designate drugs and medical devices if the following criteria are met:

4.3.1. Number of Patients:

- **a.** In Japan, the number of patients who can use medication or medical devices should be fewer than 50,000.
- **b.** Estimation of the number of patients is acquired from the report of Health and Labour Science Research or the data published by reliable scientific societies.
- **c.** If the number of patients is less than 50,000, the estimation can be taken from various statistical data.
- **d.** Since the financial year 2006, applicants may apply for orphan drug designation with the following new drugs:
  - **i.** A vaccine to prevent an infectious disease that is rarely reported in Japan or that is reported only overseas and the use of which is restricted to a specific population.
  - **ii.** A vaccine to prevent a genetic mutation-related emerging or re-emerging infectious disease, of which an outbreak has not been documented at the time of designation, but could significantly affect the lives and health of Japanese citizens [27].

4.3.2. Medical Needs: The drugs or medical devices should be recommended for the treatment of serious diseases, including difficult-to-treat diseases. Also, these drugs or medical devices should satisfy one of the following criteria for high medical needs.

- **a.** If there is no alternative relevant drug/ medical device or treatment.
- **b.** In comparison with existing products, high efficacy or safety is expected [27].

4.3.3. Possibility of Development: There should be a scientific rationale for using the product for the target disease, and the development plan should be appropriate. In the case of an orphan drug application, the possibility of development should be explained based on existing preliminary studies and clinical data in the latter half of the phase I study or in the initial stages of phase II study except where the product has already been approved overseas, or where appropriate clinical study data are available [27, 28].

4.4. Orphan Drug Designation Procedure in Japan:

Step 1: Application for Consultation: In order to procure an orphan drug/medical device designation, sponsors can submit an application for consultation at any time to the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW. The application for consultation should be filled in the Japanese language and submitted by post or fax using the Application Form for Orphan Drug/Medical Device Designation Consultation [27].

Arrangement for the Consultation Date: The administrator informs the consultation date by telephone, fax, or e-mail as soon as possible after the request for the consultation has been submitted.

Step 2: Designation Consultation: Consultation is generally held before the application of orphan designation in a 30-minute session [27].

Step 3: Process of Designation: Application forms to be submitted:

- **a.** Form 107(1) - Application for Orphan Drug Designation.
- **b.** Form 107(2) - Application for Orphan Medical Device Designation.

The content of the designation application in Japan is given in **Table 3**.

TABLE 3: CONTENTS OF THE APPLICATION TO BE SUBMITTED

S. no.	List of documents	Description
1	Data on the number of patients	Objective statistical data on the number of patients in Japan should be included
2	Data on medical needs	Data on diseases such as etiology, symptoms, and the current status such as availability of similar drugs/medical devices.
3	Data on the theoretical rationale for the use of the drugs/medical devices	Related data available at the time of application for orphan drug/medical device should be included
4	Development plan	Data on the development plan outline, including the current status, duration of the study, and necessary expenses, should be included.
5	Preparation of Summary of the Orphan Drug/Medical Device	The Summary should be prepared for Committee meetings and publication

1. The sponsors are obligated to submit an original and a copy of the application for designation to the Evaluation and Licensing Division of MHLW after the consultation. The application will be approved when it is out-and-out with all appropriate data and meets the designation requirements.

2. The Evaluation and Licensing Division of MHLW will review an orphan drug/medical device designation after receiving the application.

3. The PAFSC will be consulted if a designation can be determined.

4. A designation will be granted if the First or Second Committee on New Drugs of PAFSC approves the designation.

5. After completing all the procedures, a designation notice will be issued to the applicant, and this information is published in a government gazette as an MHLW Ministerial Notification[27].

The Orphan designation procedure in Japan is given in **Fig. 3**.

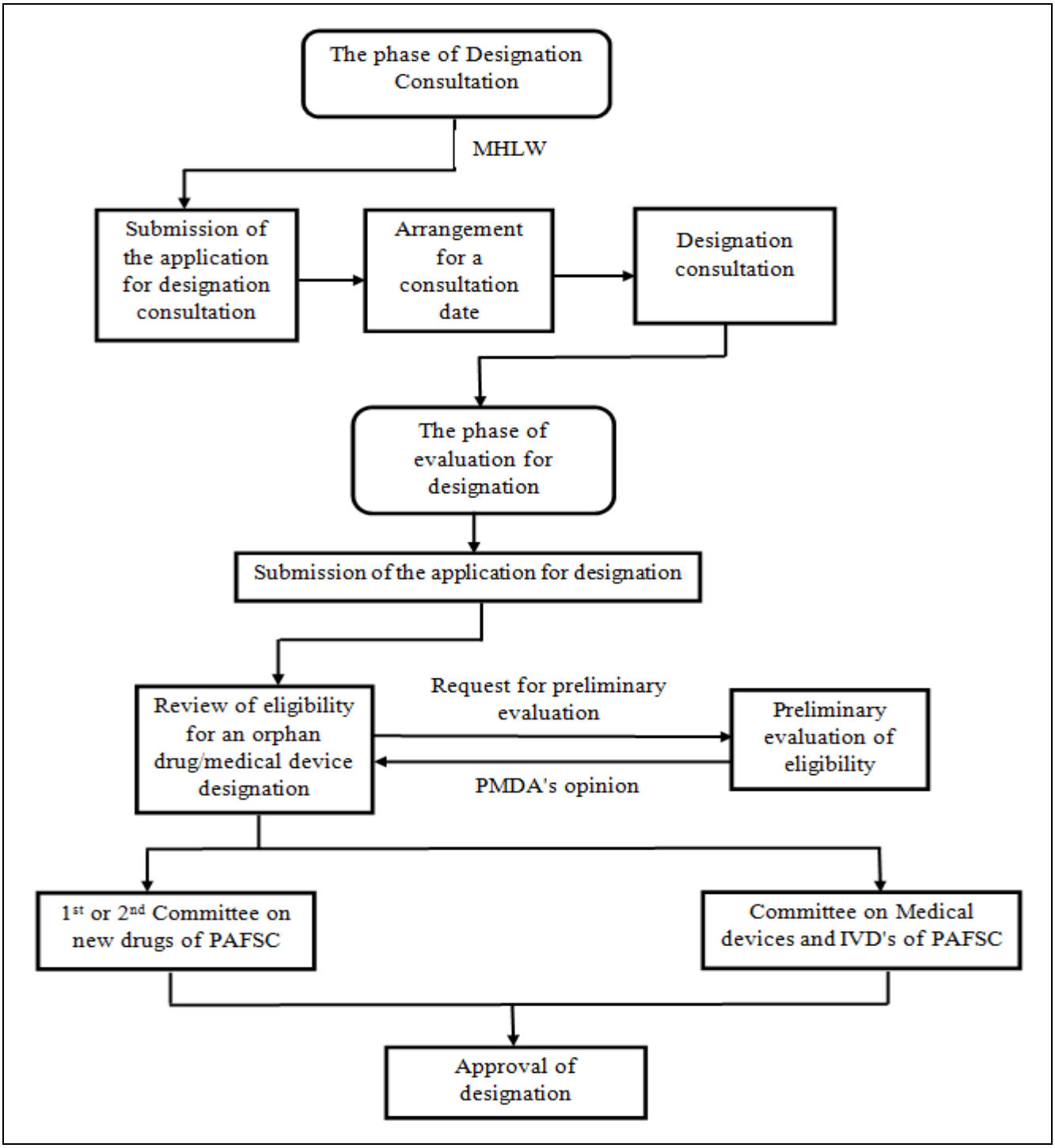

FIG. 3: ORPHAN DESIGNATION PROCEDURE IN JAPAN

4.5. Incentives:

1. Subsidy Payment: Applicants can receive subsidies through the National Institute of Biomedical Innovation (NIBIO) to reduce product development's financial burden.

2. Guidance and Consultation: Applicants can receive guidance and consultation from the MHLW, PMDA, and NIBIO on research and development activities. For a specified orphan drug/medical device, PMDA offers a priority consultation scheme.

3. Preferential Tax Treatment: *12%* of the research expenditures for orphan drugs/medical devices incurred during the NIBIO subsidy payment period can be reported as a tax credit.

4. Priority Review: The applicant should have a clear product development plan and scientific rationale to support the drug's necessity in Japan.

Once clinical trials are completed, a New Drug Application (NDA) can be submitted. Designated products will be subject to a priority review for marketing authorization. Under Priority Review designation, MHLW's goal is to take action on an application within six months (compared to 10 months under standard review) [27, 29].

5. Extension of Re-examination Period: The re-examination period will be extended to *10* years for drugs and *7* years for medical devices [27, 28].

5. Orphan Drug Regulations in Australia: In *1989* the Therapeutic Goods Act was amended in Australia to include some incentives which would encourage Australian pharmaceutical companies to develop orphan drugs. However, the full orphan drug policy was established in 1997 [26].

As outlined in 16H of Therapeutic Goods Regulations 1990, Orphan drugs are defined as "medicines, vaccines or in vivo diagnostic agent, which is intended to prevent or treat people with rare diseases, or not commercially viable to supply to treat, prevent or diagnose another disease or condition."It is not an orphan drug if it has been registered before 1 January 1998. Nevertheless, it may be registered before 1 January 1998 for another use or indication [30].

5.1. Orphan Drug Policy: The orphan drugs program, inaugurated in 1997, is considered a joint community service or public health obligation of the government and the prescription industry. The program was intended to provide an incentive for sponsors to bring medicines for a small population to market [31]. The program was designed based on the United States program, adapted only to meet Australian conditions. An official treaty was established between the FDA Office of Orphan Drug Products and the Australian TGA. This Australian program's advantage is that if a product has been evaluated in the US, then under the interagency treaty, TGA can access the evaluation report. This report is used as the basis for the review in Australia [25]. When the scheme was commenced in 1997, the prevalence criteria for a rare disease or condition was framed as less than 2,000 persons at any time based on the total population of Australia at that time, *i.e.*, approximately 20 million. However, later, as the Australian population has steadily increased, there is a need to revise the prevalence rate. For example, in 2009–2010, approximately 1800 patients suffered from Factor VIII deficiency, and later this group exceeds the numbers over 2000, thus going beyond the threshold of rare disease. Rare Voices Australia, the peak body representing Australians with rare diseases, defines a rare disease as one with an estimated prevalence of 5 in 10,000 combined with a high level of complexity [32].

5.2 Incentives: In Australia, the current incentives include the waiver of fees for evaluation, registration, and an application to the Pharmaceutical Benefits Advisory Committee (PBAC), which advises about the agent's listing on the Pharmaceutical Benefits Scheme [32]. However, Regulatory assistance is also provided to the sponsors and can be considered as an incentive. In addition to these, with the Pharmaceutical Benefits Scheme's help, subsidies are provided to enhance the drug's affordability.

5.3. Applying for Orphan Drug Designation: In the framework of Regulation 16J of the Therapeutic Goods Regulations 1990, TGA is responsible for deciding the orphan drug designation application. Once the TGA grants the orphan designation, then the application fee and the evaluation fees are waived. However, orphan drug designation granting does not infer the registration on the Australian Register of Therapeutic Goods (ARTG) [33].

5.4. Eligibility Criteria of Orphan Drug Designation: The orphan drug program eligibility criteria are laid down in Regulation *16J* of the Therapeutic Goods Regulations *1990*. An orphan designation may be granted for:

a. Previously unregistered medicine.

b. An already registered medicine with a new orphan indication, a new dosage form medicine, or a significant variation application that meets all relevant criteria, including the significant benefit criterion [34].

A medicine, including vaccines or *in-vivo* diagnostic agents, may be eligible for orphan drug designation. Orphan drug eligibility criteria in Australia are given in **Table 4**.

TABLE 4: ORPHAN DRUG ELIGIBILITY CRITERIA IN AUSTRALIA

Application Type	Standard orphan drug regulation 16J (3)	New dosage form medicine regulation 16J (4)
One indication	The application is only for one indication.	-
Serious condition	The indication is the treatment, prevention, or diagnosis of a life-threatening or seriously debilitating condition in a particular class of patients (the relevant patient class)	The indication is the treatment, prevention, or diagnosis of a life-threatening or seriously debilitating condition
Medical Plausibility	It is medically plausible if the medicine could effectively treat, prevent, or diagnose the condition in the relevant patient class	-
Orphan drug prevalence threshold or lack of financial viability	At least one of the following applies: If the medicine is intended to treat the condition that affects fewer than 5 in *10,000* individuals in Australia when the application is made It is not likely to be financially viable for the sponsor to market the medicine in Australia unless each fee referred to in paragraph *45(12)(c)* of the Therapeutic Goods regulations were waived	It is not likely to be financially viable for the sponsor to market the medicine in Australia unless each fee referred to in paragraph *45(12)(c)* of the Therapeutic Goods regulations were waived.
Refusal to approve on the grounds of safety	It is not considered an orphan drug if any of the following bodies have refused to approve the product-based safety grounds: The Secretary The United States Food and Drug Administration The European Medicines Agency Health Canada The Medicines and Healthcare Products Regulatory Agency of the United Kingdom.	
Comparison with existing therapeutic goods	No therapeutic goods that are intended to treat, prevent or diagnose the condition are included in the Register; or If one or more therapeutic goods intended to treat, prevent or diagnose the condition are included in the Register - the medicine provides a significant benefit concerning the efficacy or safety, or a significant contribution to patient care, compared to those goods	

5.5. Content of the Designation Application: The main body of the designation application should be no more than 30 pages. The Content of the designation application in Australia is given in **Table 5**.

TABLE 5: CONTENT OF THE DESIGNATION APPLICATION IN AUSTRALIA

S. no.	Content	Description
1	Summary of the condition	A clear description of the disease or condition. Details of the proposed orphan indication and therapeutic indication at registration Medical plausibility: Clinical data are required to support the rationale for developing orphan medicine in the proposed condition Use of biomarkers to subset a condition: Sub-setting a condition using biomarkers will not be accepted unless the sponsor provides substantial scientific evidence that the product's activity would not be shown on the larger population
2	Life-threatening or seriously disabling nature of the condition	Justification on seriously debilitating or life-threatening nature, based on reliable and quantifiable clinical or epidemiological information
3	Condition's prevalence or lack of financial viability	Orphan condition prevalence calculated for the condition as applied for in the designation application The methodology for the calculation should be clearly described. Up-to-date prevalence reference documentation In the case of designation applications based on the financial viability of the medicine: A justification for the lack of financial viability; Information about costs incurred or expected to be incurred in the course of developing, producing, marketing, and supplying the product; details of any grants, tax incentives or other incentives received in Australia
4	Comparison against registered therapeutic goods for diagnosis, prevention, or treatment in Australia	Details of any registered therapeutic products to diagnose, prevent, or treat the relevant indication Justification of a significant benefit in terms of increased efficacy or safety or significant contribution to patient care.
5	Description of product development	The current development status of the proposed orphan medication should be listed briefly

5.6. Orphan Drug Designation Procedure in Australia:

Step 1: Arranging a Pre-Submission Meeting: The sponsor may solicit a pre-submission meeting with TGA to address a proposed orphan drug designation application and eventual submission for registration. These meetings should occur in six months preceding the date of the sponsor plan to submit the registration application. Details of the pre-submission discussions should be provided in the Pre-submission Planning Form (PPF) and the dossier (Module 1.7.1) [33].

Step 2: Access to TGA Business Services (TBS): Designation applications shall be drawn up and submitted by persons with Submitter Access through the TGA Business Services portal. The sponsor will need the following in order to access the portal, create and submit applications:

- **a.** A TGA Client Identification (Client ID) number.
- **b.** Password access to the TGA Business services portal.
- **c.** Submitter access to the TBS portal [33].

Step 3: Submitting the Designation Application: It is recommended to submit the designation application three months prior to the date that the sponsor plans to submit for registration. Under section *16H (2)* of the Regulations, the designation application must be submitted using the approved form (the designation/determination application e-form). The sponsor can access the designation/ determination application e-form through the TBS account [33].

Ensuring that Active Ingredient(s) have an Approved Name: Each active ingredient should have one of the following approved terms:

- **a.** Australian Approved Name (AAN)
- **b.** Australian Approved Biological Name (ABN)

In the orphan drug designation application, sponsors must use the approved ingredient name(s). There is no charge for submitting an orphan drug designation application. However, the fee should be paid for priority determination or provisional determination. This fee will be refunded if the orphan drug designation is approved [33].

Step 4: TGA Assessment of the Designation Application: The target timeframe for orphan drug designation is 20 working days from receipt of an application to a decision being made [35]. After submitting the designation application using the e-form, TGA will check the information provided and confirm whether it is sufficient to assess the application. It may request the applicant for further information if needed. Application for designation is reviewed against the eligibility criteria set out in sub-regulation 16J (3) or (4) of Therapeutic Goods Regulations, depending on the application type**.** TGA's Chief Medical Advisor, the delegated decision-maker for orphan designations, will receive a recommendation from the relevant Clinical Evaluation Unit. During the assessment, the agency may request the applicant for additional information or clarification. The usual time frame for the applicant's response will be approximately 5 working days. If no response is received in the specified period, TGA will decide based on the available information [33].

Step 5: Notifying Sponsors of the Designation Decision: If the designation application meets the eligibility criteria, the medicine will be designated as an orphan drug. After making a decision, the agency will issue a decision letter to the sponsor regarding the decision. According to Regulation 48, the orphan drug designation decision is appealable. Appeals in favor of designation decisions must be lodged within 90 days of the designation decision being issued. If an orphan drug designation is approved, the agency will publish details of the eligible designation decision on the TGA website. Orphan drug designation comes into force when made and remains in force for six months as per sub-regulation 16K (1) of the Regulations unless extended or revoked [33].

Applying for an Extension of the Designation: If the sponsor was unable to lodge the submission for registration within the initial six-month span of validity, the sponsor might submit a written request to TGA to extend the orphan drug designation. Approved extensions will be granted for six months, as set out in sub-regulation 16L(1). Applications for an extension of orphan drugs

status must be lodged in the approved form at least 28 calendar days before the designation expires. Decisions regarding a refusal to extend an orphan drug designation can be appealed under Regulation 48. According to sub-regulation 16L (4) (a), an orphan drug designation cannot be extended if TGA has previously approved an extension [33].

Step 6: Applying for Registration: The orphan drug registration can be done through prescription medicines itself. However, the sponsor can apply for provisional determination and priority review determination via determination process 16R (1) for the medicines that benefit the patients. To be eligible for a waiver of registration fees, a related orphan status must be in force. Fees for minor variations to the registration of a medicine cannot be waived for an orphan drug [33].

The Orphan designation procedure in Australia is shown in **Fig. 4**.

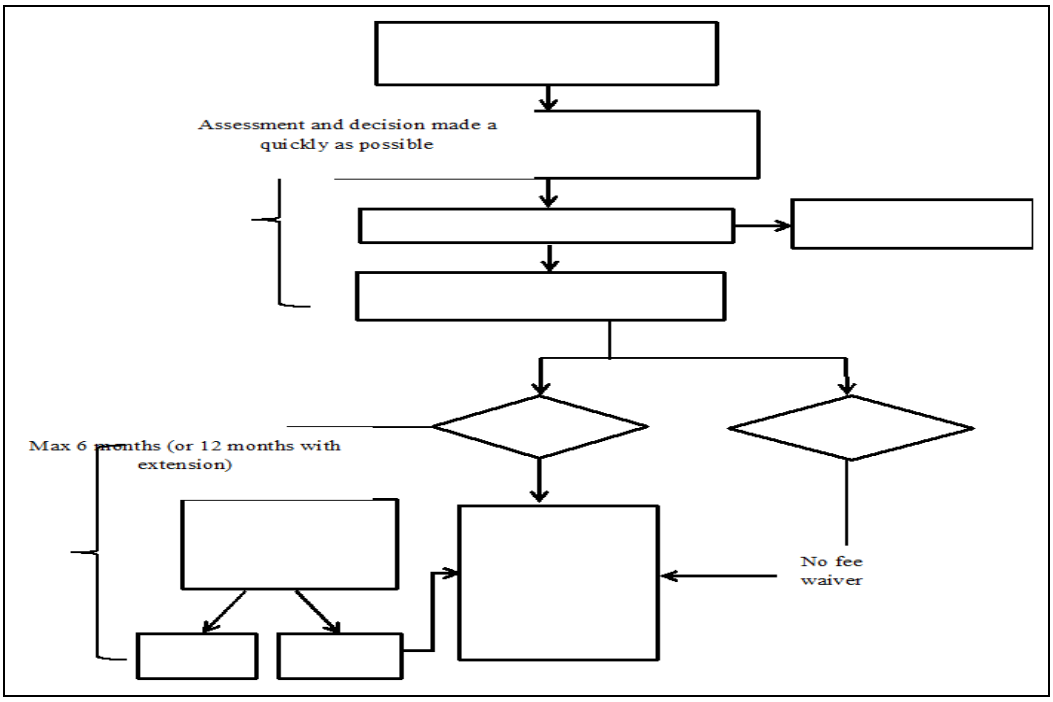

FIG. 4: ORPHAN DESIGNATION PROCEDURE IN AUSTRALIA

TABLE 6: COMPARISON OF ORPHAN DRUG REGULATIONS IN THE US, EU, JAPAN, AND AUSTRALIA

Parameters	US	EU	Japan	Australia
Legal Framework	Orphan Drug Act (ODA - 1983)	Commission regulation EC no 141/2000	Orphan Drug Regulation (1993)	Orphan Drug Policy (1997)
Responsible Authority	FDA's OOPD	EMA, COMP	MHLW, PMDA, NIBIO	TGA
Prevalence criteria	Fewer than 2,00,000 persons in the US population	Less than 5 in 10,000 persons in the Community	Less than 50,000 persons in Japan	Fewer than 5 in 10,000 individuals in Australia
The review period of the designation procedure	Typically, 90 days	Maximum of 90-day procedure	Not specified	20 working days from receipt of an application
Annual reports	Should be submitted within 14 months after the orphan drug designation was granted and annually thereafter until marketing approval.	Should be submitted within two months following the anniversary of the approved designation.	Not specified	Not specified
Protocol assistance	Yes	Yes	Yes	Yes
Reduced/ waived	Yes	Yes	Yes	Yes

regulatory fee				
Tax credits	50% for clinical studies	Managed by the member states	12% of study expenses incurred during the NIBIO subsidy payment period	No
Research grants	Programs by NIH and other agencies	"FP6" + National measures	Governmental funds	No
Marketing exclusivity	Seven years + 6 months in case of pediatric exclusivity	Ten years + 2 years in case of pediatric exclusivity	Ten years	Five years (similar to other drugs)
Special approval pathways	1) Fast track approval. 2) Breakthrough therapy. 3) Accelerated approval. 4) Priority review.	Accelerated assessment (via PRIME). Conditional marketing approval Compassionate use	1) Priority review 2) Fast track approval.	1) Provisional determination. 2) Priority review determination
Organizations for Rare Diseases	National organization for rare disorders (NORD)	European organization for rare diseases (EURORDIS)	Japan Patient Association	Rare Voices Australia
Pricing Reimbursement	Free 95% under Medicare-approved health plans	Based on member states Base on member states	Fixed= Cost +10% 100% (30% from insurance companies, 70% from national/ regional governments)	Fixed Reimbursement under Australia's life-saving drug program

6. Statistics of Orphan Designations and Orphan Drug Products in USA, EU, Japan and Australia: The statistics of orphan designations and orphan drug products in USA, EU, Japan and Australia is given in **Fig. 5** and **6**. The number of orphan designations and orphan drug products approved in the USA and the EU are given in **Fig. 7** and **8**.

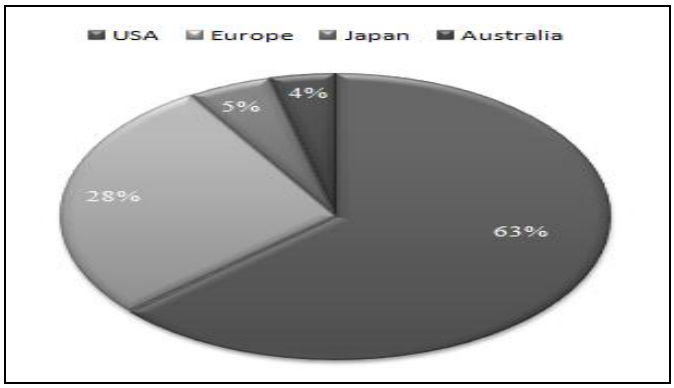

FIG. 5: PIE-CHART REPRESENTATION OF ORPHAN DESIGNATIONS APPROVED UNTIL 2019 [31, 36-39]

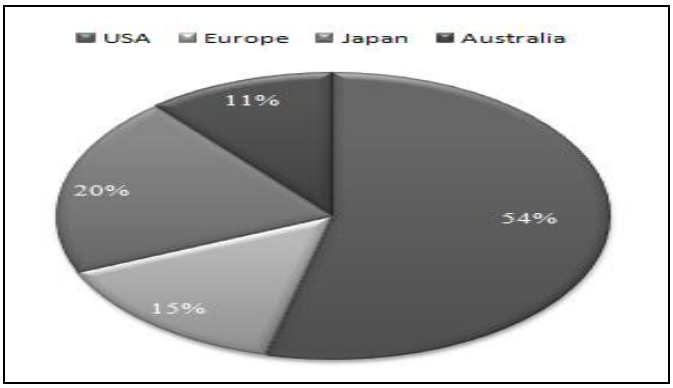

FIG. 6: PIE-CHART REPRESENTATION OF ORPHAN DRUG PRODUCTS APPROVED UNTIL 2019 [31, 36, 38-40]

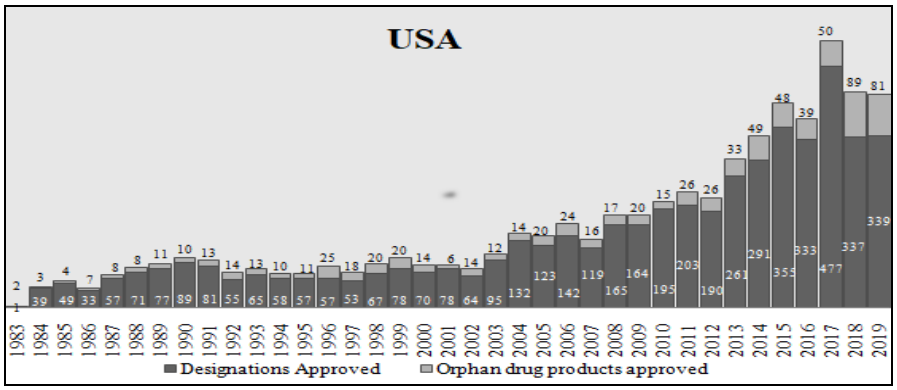

FIG. 7: GRAPHICAL REPRESENTATION OF ORPHAN DESIGNATIONS AND ORPHAN DRUG PRODUCTS APPROVED IN THE USA [36]

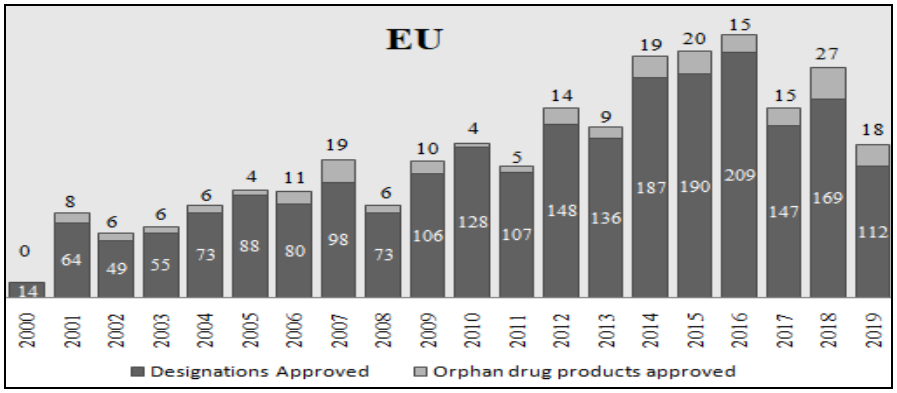

FIG. 8: GRAPHICAL REPRESENTATION OF ORPHAN DESIGNATIONS AND ORPHAN DRUG PRODUCTS APPROVED IN THE EU [37, 40]

7. Challenges: Rare diseases present radically different challenges from those of more common diseases.

7.1. Limited Scientific Knowledge:

Challenge: For many rare diseases, the cause of the disease, pathophysiology, natural course of the disease, and epidemiological data are limited or not available. This significantly hinders the ability to both diagnose and treat these diseases [41]. Due to the lack of proper understanding of the disease's natural history and heterogeneous disease phenotype and clinical course, it is challenging to select a study design and execution. Thus, a better understanding of the disease's natural history would enhance trial design, particularly in disease-stage stratification [42].

Recommendation: To address this challenge, public funding of fundamental research into the disease process is essential both nationally and globally. Rare disease patients are spread across different countries. Therefore, medical proficiency in each of these diseases is a rare resource. Investments in fundamental research must go together with investments in dedicated infrastructure and international networks (bio-banks, registries, networks of expertise). These networks may also provide opportunities to train health professionals on rare diseases. It is also equally essential to frame an internationally recognized rare disease classification system, which generates reliable epidemiological data [41].

7.2. Patient Recruitment Challenges:

Challenge: Low number of affected patients may lead to increased efforts and costs in patient recruitment for clinical studies. In a conventional model, the patients visiting the sites face more inconvenience because they may travel long distances. The sponsors conducting the study should invest more money in lodging and traveling, not only for the patients but also for their caretakers, to prevent the patient drop-out rate. This is a burden on the overall study budget [43]. Typical randomized placebo-controlled clinical trials might not be possible in conducting clinical trials for rare diseases, particularly when considering the pediatric population. The geographical dispersal of a small number of patients in orphan drug trials can pose a challenge for clinical trial execution [42].

Recommendation: The traditional patient recruitment methods should be slightly altered and should employ a more patient-centric approach. Instead of launching sites across several locations and waiting for patients to enroll, site activation can focus on the specific rare disease prevalence. This would elevate cost savings, as well as keep the timeline free of delay. In-home clinical trial support was brought to practice in clinical trials a decade ago. This model considers the patients' personal preferences, disease symptoms, and difficulties in traveling a long distance to sites while designing a clinical trial protocol. In-home clinical trial support program, CROs provide a network of hospitals and nurses or clinicians trained in GCP in various parts of the world. According to the protocol, the nurses travel to the patient's home and administer drug infusions, perform blood draws, PK sampling, or clinical tests required for the study. This method is beneficial in pediatric or neonatal clinical trials where procedures can be conducted at home or at the hospital, depending on the patient's convenience. This results in fewer visits and less

travel for the rare disease patients, thus saving the travel and lodging costs borne by the sponsors [43].

7.2.1. Utilizing Patient Registries: Patient registries are created through the collaboration between different nations like the US (NORD), Europe (EURORDIS), and Canada (CORD). These patient registries are web-based data repositories comprising as many geographies as possible with patient treatment-related health details, biological sample data, and their corresponding bio-banks with a Global Unique Identifier (GUID) to enable patient information monitoring. These communities can exchange information regarding the clinical trials in which patients with debilitating disorders can be benefitted [43].

7.3. Regulatory Challenges:

Challenge: Though there are no much differences in approval criteria for orphan drugs and non-orphan drugs, sponsors have to prove substantial evidence of the drug's effectiveness. The limited scientific understanding of the R&D process leads to the regulatory complexity determining what evidence is adequate to support orphan drugs' approval. There are various policy issues regarding the epidemiological data, including the prevalence data, which supports an orphan designation for an investigational or an already approved drug [42, 44].

Recommendation: Close collaboration with regulatory authorities might contribute to an improved and highly individualized path to drug development and registration[42.]

7.4. High Prices:

Challenge: Due to the growing number of orphan drugs in the market, there is an impact on orphan drug pricing and reimbursement [42]. The affordability of orphan drugs has become a significant issue for payers and stakeholders [29]. Resource use and treatment costs are also challenging because very few clinical centers are specialized in diagnosing and treating rare diseases [46].

Recommendation: Orphan drugs can be reimbursed from public funds accessible to patients because these drugs' prices are higher than those for common diseases [46]. A transparent and evidence-based approach is required for the pricing and reimbursement of orphan drugs. It is also recommended to use a low-cost delivery model that aids the delivery of orphan drugs by specialty pharmacies to the relevant patients. Specialty pharmacies make the complex reimbursement process easier for patients, providers, and payers [47].

CONCLUSION: The field of rare diseases experiences a shortage of sufficient medical knowledge. For a long time, doctors, researchers, and policymakers were unaware of rare diseases. There was no real exploration in research or public health policy concerning the field's issues until recently. Besides the benefits of more extended marketing exclusivity, waived regulatory fees, R&D grants, tax credits, fast approval, premium pricing, shorter developmental timelines, *etc*., orphan drugs also include challenges like limited scientific knowledge, low number of patients available, high pricing of these drugs & other regulatory challenges. More orphan drugs have been developed and approved after the ODA's enforcement in the USA and similar legislation in other countries.

Designation criteria like Life-threatening or seriously debilitating conditions of disease, Medical plausibility, lack of commercial viability are similar among the USA, EU, Japan, and Australia. However, the prevalence criteria are not internationally harmonized; thus, it also varies among these four nations. Orphan legislation offers essential incentives to invigorate the development of medicinal products for rare diseases, thus demonstrating the legislation's success. However, Australia is deficient in providing incentives when compared to the USA, EU, and Japan.

The Orphan drug legislation in various countries have not only contributed to new drugs for patients for an extended period which has no attention from researchers and the pharmaceutical industry, but it has also contributed to society in a broader context; for example, the EU legislation has not only helped companies to invest resources in the field of rare diseases but also in the creation of new companies. Health care services have also been influenced by the introduction of orphan drug legislation in terms of the high benefit to patient families and the increase in medical experience in rare diseases and establishing the research networks and facilities, thereby promoting the exchange of information.

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REFERENCES:

1. National policy for treatment of rare diseases [Internet]. 2020 [cited 27 October 2020]. Available from: https://main.mohfw.gov.in/sites/default/files/Rare%20Diseases%20Policy%20FINAL.pdf .
2. Rare disease [Internet]. En.wikipedia.org. 2020 [cited 20 October 2020]. Available from: https://en.wikipedia.org/wiki/Rare_disease .
3. Orphan Drugs Market: Rising Prevalence of Rare Diseases to Strengthen the Market | Medgadget [Internet]. Medgadget.com. 2020 [cited 8 December 2020]. Available from: https://www.medgadget.com/2020/11/orphan-drugs-market-rising-prevalence-of-rare-diseases-to-strengthen-the-market.html .
4. Rashmi R: Fabry Disease: Perspectives from 5 Years of FOS. Oxford: Oxford Pharma Genesis 2006.
5. Designating an Orphan Drug or Biologic [Internet]. U.S. Food and Drug Administration. 2020 [cited 8 December 2020]. Available from: https://www.fda.gov/industry/developing-products-rare-diseases-conditions/designating-orphan-product-drugs-and-biological-products .
6. Orphan Drug Designation Request Form [Internet]. U.S. Food and Drug Administration. 2018 [cited 8 December 2020]. Available from: https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/orphan-drug-designation-request-form.
7. Hall AK and Carlson MR: The current status of orphan drug development in Europe and the US. Intractable Rare Disease Research 2014; 3(1):1-7.
8. Recommended Tips for Creating an Orphan Drug Designation Application [Internet]. Fda.gov. 2018 [cited 8 December 2020]. Available from: https://www.fda.gov/media/111762/download.
9. ORPHAN DRUGS: FDA Could Improve Designation Review Consistency; Rare Disease Drug Development Challenges Continue [Internet]. Gao.gov. 2018 [cited 8 December 2020]. Available from: https://www.gao.gov/assets/700/695765.pdf.
10. Frequently Asked Questions (FAQ) About Designating an Orphan Product [Internet]. U.S. Food and Drug Administration. 2019 [cited 8 December 2020]. Available from: https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/frequently-asked-questions-faq-about-designating-orphan-product.
11. O'Connor D: Orphan drug designation – Europe, the USA and Japan. Expert Opinion on Orphan drugs. 2013; 1: 255-59.
12. Institute of Medicine (US) 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. PMID: 21796826.
13. 21 CFR PART 316 -- ORPHAN DRUGS. Office of the Federal Register; 1999.
14. Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on Orphan Medicinal Products. European Parliament, Council of the European Union; 2000.
15. Commission Regulation (EC) No 847/2000 Of 27 April 2000 Laying Down the Provisions for Implementation of the Criteria for Designation of a Medicinal Product as an Orphan Medicinal Product and Definitions of the Concepts 'Similar Medicinal Product' and 'Clinical Superiority. European Commission; 2000.
16. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. European Parliament, Council of the European Union; 2004.
17. Commission Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council. European Commission; 2006.
18. Regulation (EC) No 1901/2006 of the European Parliament and of the council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. Provisional data; 2007.
19. Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another [Internet]. 4th ed. European Commission; 2020 [cited 28 November 2020]. p. 3. Available from: https://ec.europa.eu/health//sites/health/files/files/orphanmp/2014-03_guideline_rev4_final.pdf .
20. Applying for orphan designation - European Medicines Agency [Internet]. European Medicines Agency. 2020 [cited 26 Nov 2020]. Available from: https://www ema.europa.eu/en/human-regulatory/research-development/orphan-designation/applying-orphan-designation.
21. Procedural advice for orphan medicinal product designation [Internet]. 9th ed. European Medicines Agency; 2020 [cited 9 December 2020]. p. 6. Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/procedural-advice-orphan-medicinal-product-designation-guidance-sponsors_en.pdf .
22. Nicolodi C: Orphan drug designation in Europe-Procedural guidance and challenges. International Journal of Drug Regulatory Affairs [Internet] 2019; 7: 1-7.
23. Procedural advice for post-orphan medicinal product designation activities [Internet]. 9th ed. European Medicines Agency; 2020 [cited 28 November 2020]. p. 7. Available from: https://www.ema.europa.eu/en/documents/other/procedural-advice-post-orphan-medicinal-product-designation-activities-guidance-sponsors_en.pdf .
24. Applying for marketing authorisation: orphan medicines - European Medicines Agency [Internet]. European Medicines Agency. 2020 [cited 9 December 2020]. Available from: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/orphan-medicines/applying-marketing-authorisation-orphan-medicines#:~:text=In%20advance%20of%20marketing%20authorisation,orphan%20which%20are%20under%20market .

25. Scott D, Alder S, Usui E and Lui K: Orphan Drug Programs/Policies in Australia, Japan and Canada. Drug Information Journal 2001; 35: 1-16.
26. Franco P: Orphan drugs: the regulatory environment. Drug Discovery Today 2013; 18(3-4): 163-72.
27. Overview of Orphan Drug/Medical Device Designation System [Internet]. Mhlw.go.jp. 2020 [cited 8 December 2020]. Available from: https://www.mhlw.go.jp/english/policy/health medical/pharmaceuticals/orphan_drug.html#:~:text=In%20Japan%2C%20drugs%20and%20medical,if%20they%20are%20intended%20for .
28. Current Status and Challenges of Development for Orphan Drugs in Japan [Internet]. Pmda.go.jp. 2020 [cited 8 December 2020]. Available from: https://www.pmda.go.jp/files/000205954.pdf .
29. Sharma A, Jacob A, Tandon M and Kumar D: Orphan drug: Development trends and strategies. Journal of Pharmacy and Bioallied Sciences 2010; 2(4): 290-9.
30. Therapeutic Goods Regulations 1990. Federal Register of Legislation; 1990.
31. Therapeutic Goods Administration. Orphan drugs program discussion paper [Internet]. Australian Government; 2015 [cited 9 December 2020]. Available from: https://www.tga.gov.au/sites/default/files/consultation-orphan-drugs-program.pdf ,
32. Herkes G: Orphan drugs in Australia: Expert Opinion on Orphan Drugs [Internet] 2016; 4: 1195-97.
33. Orphan drug designation. A step-by-step guide for prescription medicines [Internet]. Therapeutic Goods Administration (TGA). 2018 [cited 9 December 2020]. Available from: https://www.tga.gov.au/publication/orphan-drug-designation .
34. Orphan Drug designation eligibility criteria [Internet]. Therapeutic Goods Administration (TGA). 2018 [cited 9 December 2020]. Available from: https://www.tga.gov.au/publication/orphan-drug-designation-eligibility-criteria .
35. What will happen with the application for designation? [Internet]. Therapeutic Goods Administration (TGA). 2016 [cited 9 December 2020]. Available from:https://www.tga.gov.au/book-page/what-will-happen-application-designation.
36. Karst KR: Orphan Drug Designation Requests and Designations Dipped in 2018, But Orphan Approvals Are Up Again! [Internet]. FDA Law Blog. 2018 [cited 10 December 2020]. Available from: https://www.fdalawblog.net/2019/03/orphan-drug-designation-requests-and-designations-dipped-in-2018-but-orphan-approvals-are-up-again.
37. Orphan Medicines Figures 2000- 2019 [Internet]. 2019 [cited 6 December 2020]. p2. Available from: https://www.ema.europa.eu/en/documents/other/orphan-medicines-figures-2000-2019_en.pdf .
38. Harada K, Toriyabe K and Ono S: Survey of Japanese Orphan Drug Program: Factors Related to Successful Marketing Approval. The Journal of Clinical Pharmacology 2019; 60: 117-24.
39. Annual performance statistics report: July 2018 to June 2019 [Internet]. 2019 [cited 6 December 2020]. p. 17. Available from: https://www.tga.gov.au/sites/default/files/annual-performance-statistics-report-july-2018-june-2019.pdf .
40. List of the latest marketing authorisations and orphan medicinal products designations | www.eurordis.org [Internet]. Eurordis.org. 2020 [cited 7 December 2020]. Available from: https://www.eurordis.org/orphan-drug-designations-marketing-authorisations .
41. Rare diseases [Internet]. 2013 [cited 7 December 2020]. Available from:
42. https://www.who.int/medicines/areas/priority_medicines/Ch6_19Rare.pdf ?
43. Fonseca D, Amaral I, Pinto A and Cotrim M: Orphan drugs: major development challenges at the clinical stage. Drug Discovery Today 2019; 24: 867-72.
44. Rare Disease Patient Recruitment and Retention [Internet]. Clinicalleader.com. 2020 [cited 9 December 2020]. Available from:https://www.clinicalleader.com/doc/rare-disease-patient-recruitment-and-retention-0001#:~:text=The%20traditional%20methods%20of%20patient,waiting%20for%20patients%20to%20enroll.
45. Shelly A and Shivali A: Rare diseases and orphan drugs: challenges, regulatory movements and market strategy (Special Focus: India) [Internet]. 2019 [cited 8 December 2020]. p. 11, 12. Available from: http://knowledgeisotopes.com/wp-content/uploads/2019/03/RareDiseases-andOrphanDrugsChallengesRegulatoryMovementsandMarketStrategySpecialFocusIndia.pdf
46. Stawowczyk E, Malinowski KP, Kawalec P, Bobiński R, Siwiec J, Panteli D, Eckhardt H, Simoens S, Agusti A, Dooms M and Pilc A: Reimbursement Status and Recommendations Related to Orphan Drugs in European Countries. Frontiers in Pharmacology 2019; 10: 1279.
47. Patel BN and Audet PR: A review of approaches for the management of specialty pharmaceuticals in the United States. Pharmacoeconomics 2014; 32(11): 1105-14.

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