ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.ijrps.com

Orphan Drug Regulation In Japan and Australia

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Article History:

Received on: 21 Jan 2020
Revised on: 26 Feb 2020
Accepted on: 04 Mar 2020

Keywords:

PMDA,
TGA,
Orphan drugs,
rare diseases

ABSTRACT

Due to various reasons, the pharmaceutical industries growth has slowed in recent years. The current economic situation has therefore shifted the pharmaceutical companies ' focus from essential medicine to the new business model called "orphan drugs". Healthcare standards are among the worlds highest in Japan. For about 99 percent of its citizens, the Japanese government provides health insurance. Rare diseases fall under 'intractable diseases (Nanbyo)' in Japan. Japan regulatory body PMDA is providing all guidance and instructions on orphan drugs. In Australia, Australia's regulatory body providing all guidance on orphan drugs to the health care system. To be named an orphan drug in Australia, the pharmaceutical company that developed the medication will show to the Orphan Drug Program that the drug is not commercially viable for such a small population of patients. Often, the Orphan Drug System reduces the amount of time it usually takes for the TGA to test a drug. Once a drug is approved as an orphan drug, it is easier for the drug to become available, and it can be obtained through the Life Saving Drugs Program in certain situations. This review study provides comparative study of guidelines for orphan drug and rare diseases regulations in Japan and Australia.

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ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11i2.2088

Production and Hosted by

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INTRODUCTION

Medicinal drugs classified as an orphan drug have been developed specifically for the treatment of a rare medical condition, which is referred to as an orphan disease. It can be described as drugs that are not produced for economic reasons by the pharmaceutical industry but that respond to the need for public health. Of orphan disease, there is no single definition. Definitions are based on the number of people affected by the disease, as well as other considerations such as disease severity and appropriate therapy. The number of patients expected to recognize a disease as an orphan disease depends on the size of the country's population. Clinically, medications and medical devices are very important to patients with rare diseases. Nonetheless, due to the small number of targeting customers, incompetence in designing these goods makes it difficult to precede successful research and development. Therefore, appropriate research and development steps for orphan medicinal products should be taken to support rare disease patients (Song *et al.*, 2012b).

Japan

Japan spends around $300 billion (US) annually on health-related costs, and Japanese customers expect healthcare healthier and better. As a result, healthcare developments were promoted in Japan, includ-

ing the production of orphan drugs and devices. In Japan, medicines and medical devices may be listed as orphan drugs or medical devices if they are intended for use in less than 50,000 patients in Japan, and for which there is a high medical need. The Ministry of Health, Labour and Welfare designates them based on the recommendation of the "Pharmaceutical Affairs and Food Sanitation Council (PAFSC)." In 1985, Japan launched an orphan therapeutic system for the first time. There were only two clauses in this 1985 notification: reduction of the data required for request and accelerated analysis. To justify the need for the medication in Japan, the applicant should have a particular product development strategy and scientific rationale. A "New Drug Application (NDA)" may be submitted after clinical trials have been completed. It is important to remember that there is room for interpretation in this law, even though Japan has orphan drug legislation. The "MHLW" takes a case-by-case determination on orphan drug status and approval. This is particularly true when deciding the number of clinical trials needed for approval in Japan. "Glaxo's Lexiva for HIV infection (Fosamprenavir), Genzyme's Fabrazyme (Agalsidase beta) for Fabry, and Novartis ' Visudyen (Verteporfin) for age-related macular degeneration" are several recently approved orphan drugs (European Commission, 2018).

Table 2 gives the basic information about the Australia and Japan

In April 1993, to incorporate the orphan medicinal drug scheme, Japan revised its "Pharmaceutical Affairs Act (PAL)". The Japanese orphan drug policy is similar to the US policy, with measures being put in place to promote orphan drug research; additionally, orphan status in Japan includes medicines, appliances, and vaccines. As of March 2008, 223 orphan drugs and 18 orphan medical devices in Japan had been given designated status, of which "147 drugs and 6 devices" were licensed for marketing. Foreign companies hold over half of these advertising authorisations (Song *et al.*, 2013). Most of Japan's orphan drugs are used to treat "infectious diseases (including HIV), haematological diseases, neuromuscular diseases, cancer, diseases of the immune system, and infant-common diseases."

Table 3 gives the details about the differences on the Australia and Japan regulatory overview (Scott *et al.*, 2001).

Criteria for orphan drug designation in Japan

1. Population – "The number of patients affected by this disease within Japanese territories must be less than 50,000, equivalent to a limit of four per 10,000 or 0.05 per cent of the population."
2. Medical need - The illness believed to be using the medication must be incurable. Any alternative therapy must be available or the proposed drug must be medically superior to medications currently on the Japanese market.
3. Development feasibility - To justify the need for the drug in Japan, applicants should have a specific product development strategy and scientific justification (Song *et al.*, 2012a)

Japanese encephalitis

Figure 1: Rare diseases in Japan- example

Figure 1, shows the rare disease example in Japan (Adachi *et al.*, 2017)

Benefits for orphan drugs

Drug companies which receive orphan drug approval in Japan are eligible for the following benefits:

1. The "MHLW (Ministry of Health, Labour and Welfare)" has a free counselling service expressly for the orphan drug designation applicants.
2. The Government of Japan provides financial assistance to applicants to collect supporting data, i.e. clinical trials, bridging studies, etc. The applicant may also receive financial assistance for up to 50% of the cost of clinical trials, as well as tax exemptions for up to 6% of the cost of research and 10% of corporate tax.
3. Drug will be put on a fast-track approval process that is usually much smoother than conventional drugs While approval of traditional

Table 1: Orphan drug designation criteria

Application type	Standard orphan drug Regulation 16J	New dosage form medicine Regulation 16J
1.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
2.Medical Plausibility	it is not medically plausible that the medicine could effectively treat, prevent or diagnose the condition in another class of patients that is not covered by the relevant patient class	-
3.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 – the condition affects fewer than 5 in 10,000 individuals in Australia when the application is made; if the medicine is intended to prevent or diagnose the condition the medicine, if it were included in the Register, would not be likely to be supplied to more than 5 in 10,000 individuals in Australia during each year that it is included in the Register; 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 in relation to the medicine	it is not likely that it would 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 1990 were waived in relation to the medicine
4. Comparison with existing therapeutic goods	either: 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 that are intended to treat, prevent or diagnose the condition are included in the Register-the medicine provides a significant benefit in relation to the efficacy or safety of the treatment, prevention or diagnosis of the condition, or a major contribution to patient care, compared to those goods.	either: 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 that are intended to treat, prevent or diagnose the condition are included in the Register-the medicine provides a significant benefit in relation to the efficacy or safety of the treatment, prevention or diagnosis of the condition, or a major contribution to patient care, compared to those goods.

Table 2: Australia V/S Japan

Country	Australia	Japan
Capital	Canberra	Tokyo
Currency	Australian dollar (AUD)	Japanese Yen
Language	English	Japanese, English
Regulatory authority	Therapeutic Goods Administration (TGA)	Pharmaceuticals and Medical Devices Agency (PMDA)

Table 3: Australia V/S Japan -Regulatory Prespective on Orphan Drugs

Country	Australia	Japan
Program Established	1998- development in collaboration with united states FDA; formal agreement established for exchange and review of information.	1993- pharmaceutical affairs law amended to promote systems for orphan drug development.
Products eligible for orphan designation	Drugs and biologics (include vaccines and in vivo diagnostics)	Drugs, biologics and devices
Market exclusivity	Not applicable, although de facto exclusivity possible since the second product with the same active ingredient will not be designated unless clinical superiority is shown.	extended re-examination term (2nd sponsor must conduct full development program during this time)
Regulatory fees	Marketing application and designation fees; waived other fees can be reduced.	Application fees reduced.
Financial incentives for research and development	not applicable	Grants for up to 50% of yearly R&D costs available up to 3 years; authorization for tax deductions for preclinical and clinical research.
Other benefits	Shorter review time than statutory 255 working days expected; FDA evaluation reports will facilitate review.	Accelerated review process; guidance on development.

drugs takes at least 12 months, the fast-track approval process will in principle take 10 months. Renewal of the orphan drug brand is on other products every 10 years compared to every 6 years (Sharma *et al.*, 2010).

The "MHLW" determines on a case-by-case basis the amount of clinical data required to apply and authorize an orphan drug. Japanese information is, of course, the most important. Japanese data are considered to help the approval of the drug. Generally speaking, the "MHLW" uses foreign or non-Japanese (Asiatic) data more as reference data. In Japan, as in other Asian countries, it is especially important to identify doctors or "Key opinion leaders (KOLs)" who may be interested in your orphan drug. It is aimed at physicians who focus on the particular illness / condition of drug treatments to achieve the best product support. It may also be very important to support related Japanese organisations (Song *et al.*, 2012b).

Organizations that designates orphan drugs

MHLW

1. Review and designation- orphan drugs /medical devices
2. Review and approval – orphan drugs/ medical devices
3. Pre-designation consultation – orphan drugs/ medical devices
4. Operational cost payment for National Institute of Biomedical Innovation (NIBIO).

The outline process for orphan drug / medical device designation in Japan is depicted in Figure 2. (European Medicines Agency, 2020).

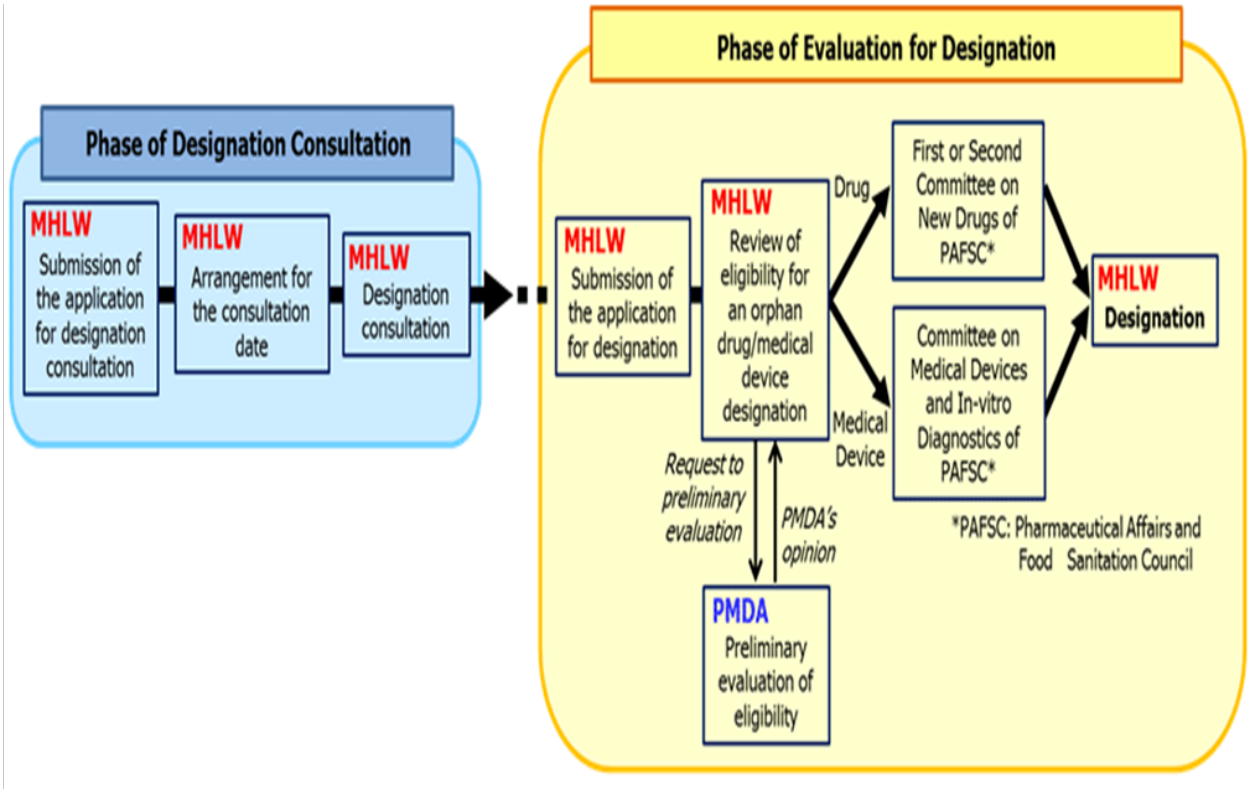

Figure 2: Outline of process for orphan drug / medical device designation in Japan

PMDA

Priority expert review for orphan drugs / medical devices for clinical trials and advertising authorisation dossiers.

National Institute of Biomedical Innovation (NIBIO)

1. Subsidy fee to the applicant
2. Accreditation of applicant's work costs
3. Guidance and advice to the applicant (Song *et al.*, 2012a).

Figure 3, shows the rare disease patient with muscular dystrophy (TGA, 2018).

Muscular dystrophy

Figure 3: Examples for rare diseases in Australia

Orphan drug designation procedure

After the assessment, the applicant will apply to MHLW's Pharmaceutical and Food Safety Bureau (PFSB) an initial and also a copy of the request for appointment.

The request for the designation of an orphan should be made in Japanese. The Evaluation and Licensing Division will review the submitted application and consult "PAFSC" if a designation can be determined.

In practice, A status shall be granted if accepted by the First or Second Committee on New Drugs (or the Committee on Medical Devices and In-vitro Diagnostics for orphan medical devices) of "PAFSC".

The designation notice will be sent to the applicant after all the procedures have been completed. The

The above flow chart of Figure 4, explains the process of drug designation (TGA, 2018).

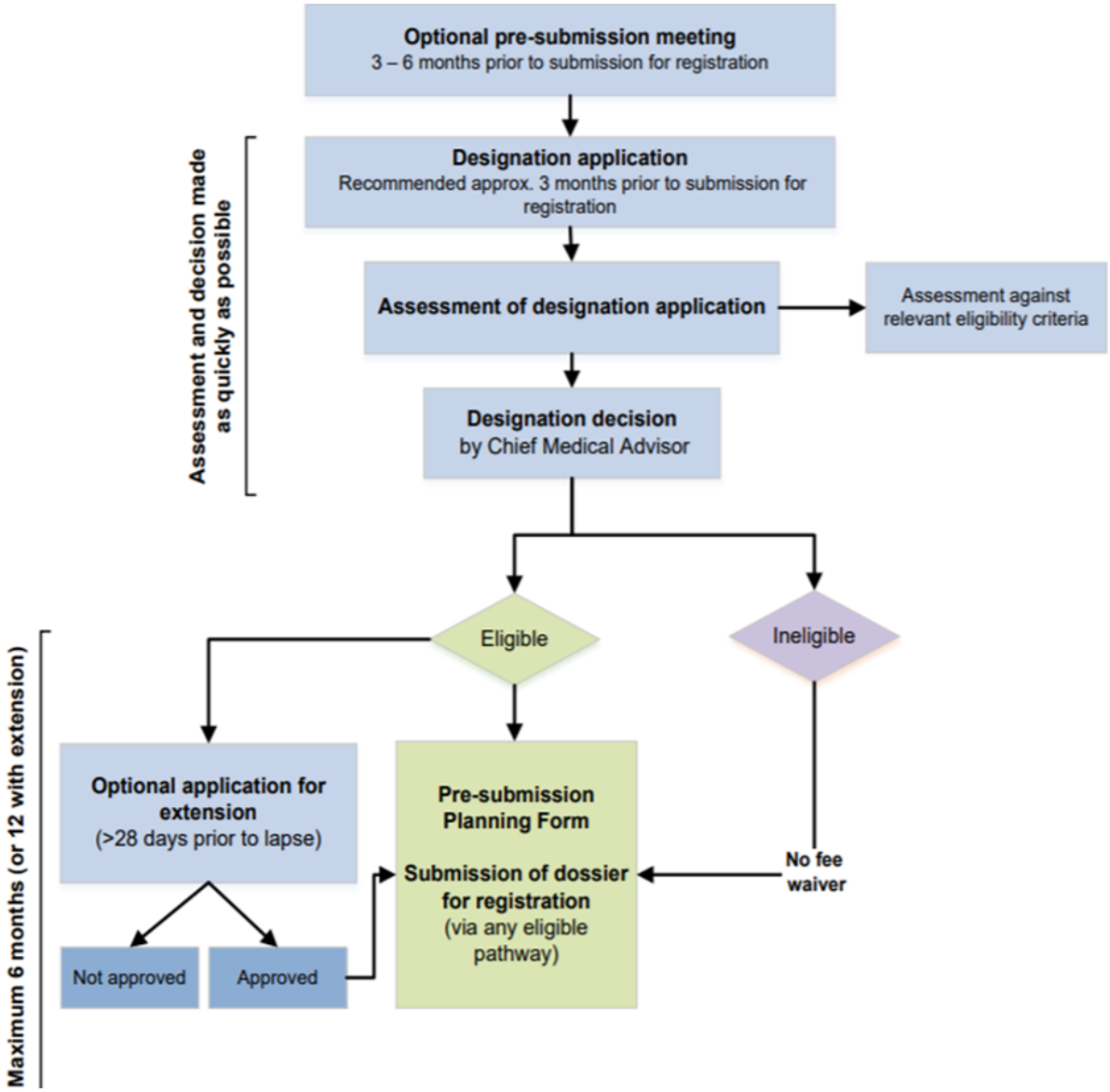

Figure 4: Flowchart of Orphan Drug Designation process in Australia (TGA)

designation will be released as a "MHLW" Ministerial Notification in a government gazette (European Medicines Agency, 2020).

Incentives

Financial Incentives

1. "National Institute of Biomedical Innovation (NIBIO)" — provides orphan product development grants "up to 50% of R&D costs".
2. Government funds, for instance the Symptoms Alleviation and Exploration Advancement Medication Store, are widely used to guarantee this test.
3. An individual who has earned R&D subsidies shall not be entitled to repay NIBIO if the orphan product sales are less than 100 million.
4. If the product sales reach 100 million- "the applicant shall pay 1% of the total above 100 million to NIBIO for the first 10 years or until the subsidy has been repaid."
5. Regulatory meetings: "NIBIO" provides free guidance on the nature of clinical trials.
6. User fees-" 25% reduction in initial regulatory user fees (review of the user for marketing).

The above flowchart of Figure 5, explains the orphan drug registration in Australia (TGA, 2018).

Administrative Incentives

The key administrative benefits offered to companies seeking orphan drug status are assistance with production consultation, accelerated approval and extended market exclusivity (European Commission, 2018).

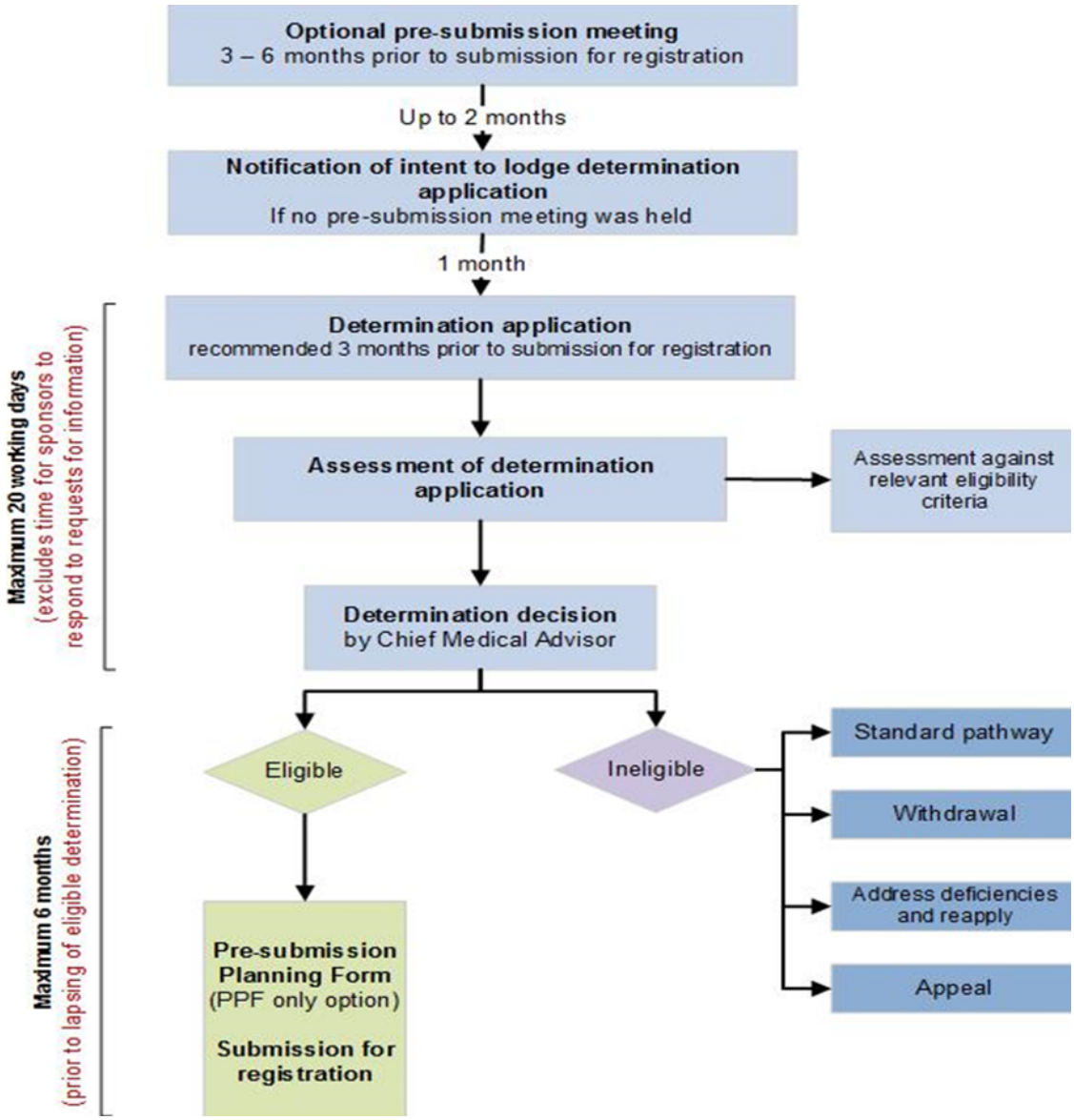

Figure 5: Flowchart of Orphan Drug Registration in Australia (TGA)

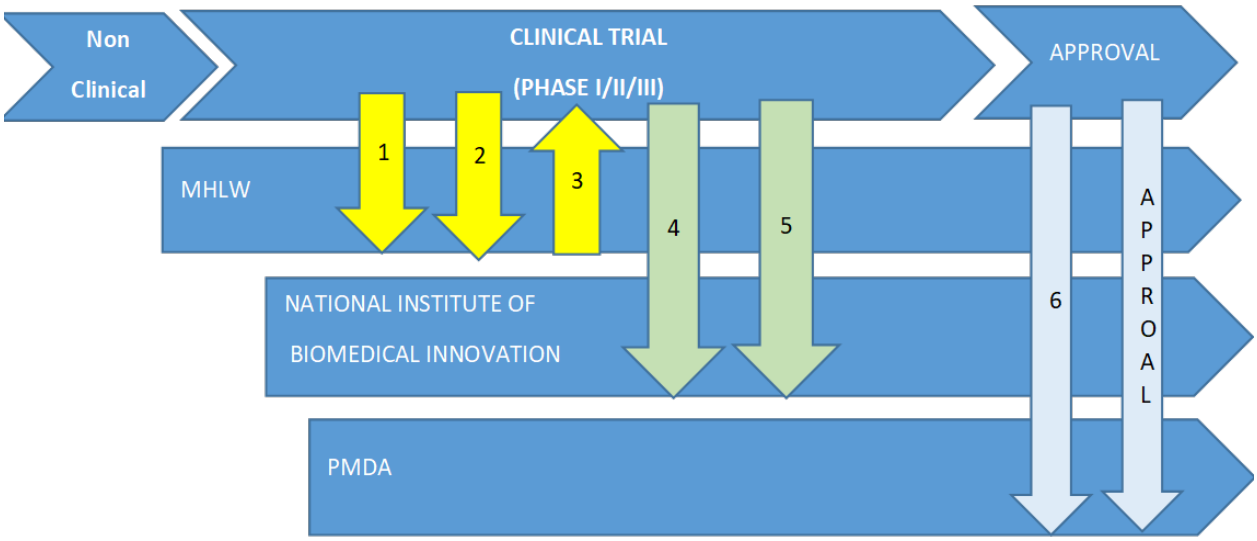

Figure 6: Orphan Drug Registration process in Japan

Figure 6, shows the orphan drug registration pro

1. Orphan drug consultation
2. Orphan drug application
3. Appointed as an orphan drug
4. Grant application
5. Money granted
6. Approval application

cess in Japan. The numbering indicates the process which are mentioned in Figure 6 (European Commission, 2018).

Australia

Australia's "Orphan Drug Program," initiated in 1998. The program's purpose is to enable sponsors to produce and sell drugs for rare disease care, prevention and diagnosis. Australia's federal government recognizes that pharmaceutical producers are reluctant to produce such drugs because the cost of production and distribution is not financially advantageous. The Orphan Drug Program was set up to solve this issue and ensure access to drugs of the same importance, efficacy, and safety as infectious disease patients. The plan's legal basis is Part 3B of the Therapeutic Goods Regulations, 1990. The program is funded by the Therapeutic Goods Administration (TGA). Marketing approval of an orphan drug product in Australia requires two phases: an initial application for the medication to be classified as an orphan, based on the occurrence of a specific disease or commercial non-availability, followed by a price, safety and efficacy review application for product registration (Herkes, 2016).

In Australia, orphan drugs are medications which are used at any time to treat diseases or conditions that affect less than 2,000 individuals. The application must show why the medicine is an orphan drug to receive the orphan designation (TGA, 2018). A medicine, including vaccines or in vivo diagnostic agents, may be eligible for orphan drug designation if all orphan criteria in the Table 1 are satisfied (regulation 16J of the Therapeutic Goods Regulations 1990 (the Regulations)). (Table 1 gives in detail information about the orphan drug designation criteria in Australia) (TGA, 2018).

CONCLUSIONS

Research has shown that benefits provided by legislation on orphan drugs are important and can promote the production of orphan drugs to support rare disease patients. In Japan, since specific orphan drug legislation was enacted in 1993, the number of approved orphan drugs has increased. Orphan drugs are licensed at a higher rate for marketing than in the United States or the EU. Multiple orphan drug regulatory strategies and rare disease research were also adopted as part of the national health system with extensive support from the Japanese government. These movements facilitate access to orphan drugs, promote orphan drug research and development, and an information centre supported by the government to foster understanding of rare diseases. In addition, a project was launched in 2013 with government support to establish a national rare disease database to collect a wide range of information on rare disease patients. The quality national data given will lead to new avenues for research and treatment of rare diseases as well as encouraging the discovery in the near future of orphan drugs. The Australian Orphan Drug Program has actively facilitated the development and marketing of medicines in Australia for the treatment of rare diseases. Since its introduction in 1998, the policy standards have remained unchanged and there are no proposals for further updates or improvements to TGA's current business reform program.

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