Niveditha Neelakandan et al /J. Pharm. Sci. & Res. Vol. 11(11), 2019, 3592-3598

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Orphan Drug Designation in Australia

Niveditha Neelakandan, D. Nagasamy Venkatesh*, Ann Lydia Gomez
Dept of Pharmaceutical Regulatory Affairs,
JSS College of Pharmacy,
(JSS Academy of Higher Education & Research)
Ooty-643 001. Tamil Nadu. India.

Abstract

Aim: The definition of orphan disease depends on the legislation and policies adopted by each region or country with reference to the population affected by the disease, the Therapeutics Goods Administration (TGA) defines rare disease as a disease, or condition, likely to affect not more than 2,000 individuals in Australia at any time. The Australian government commenced the Orphan Drugs Program in the year 1997 with an objective to encourage the pharmaceutical companies to produce orphan drugs. The main objective is to describe and discuss the legal framework to obtain the designation for the orphan drugs in Australia.

Conclusion: It is important to understand the progress of the Australian legislative systems to improve the collaboration in the field of orphan drugs and rare diseases.

Keywords: Rare disease, TGA, orphan drugs program, orphan drug designation.

INTRODUCTION

The orphan diseases are rare diseases which affects a very small population. According to the WHO definition the rare diseases affects one out of 2000 people or less. The orphan diseases are genetic, chronic and debilitating diseases. Approximately there are 5000 to 8000 orphan diseases or rare diseases out which most are said to be genetic. An estimate across the globe states that there will be one person affected by a rare disease among 15 people which describes that among 400 million people worldwide 30 million Europeans and 25 million Americans would be affected. [1] On the whole the rare diseases affect a very few populations. The orphan disease definition differs from country to country and their respective regulations with respect to the occurrence of the disease in a population,[2] the Regulation 2 of the Therapeutic Goods Regulation of Australia defines orphan diseases as the disease or condition likely to affect not more than 2000 individuals in Australia at any time. [3]

Orphan drugs program

The orphan drugs program is considered as a joint community service or public health obligation of the government and the prescription industry it was commenced in the year 1997. The main objective of this program is to bring the orphan drugs into the Australian market for the small population by providing incentives to the pharmaceutical industries.[3] With an aim to bring the orphan drugs for the smaller population in Australia, firstly for the orphan drug to be available in the Australian market it should go through the evaluation process to receive a final approval from the Australian regulatory agency TGA (Therapeutic Goods Administration). During the evaluation process the orphan drugs are tested for their quality, safety and efficacy. There are expenses involved for conducting the evaluation studies in case of the orphan drugs these expenses have been waived. Thereby the incentive provided by the orphan drugs program to the pharmaceutical company is the waiving of the evaluation fee hence it encourages the industries to have their orphan drug evaluated. In Australia for a drug to be designated as orphan drug, the pharmaceutical industry should demonstrate that the drug is not commercially viable and its intended for use only by a small patient population. [4]
According to the 16 H of the Therapeutic Goods Regulation orphan drug is defined as;

1. A medicine, vaccine or in vivo diagnostic agent is an ***orphan drug*** if it complies with this regulation.
2. It:
   a. must be intended to treat, prevent or diagnose a rare disease;
      or
   b. must not be commercially viable to supply to treat, prevent or diagnose another disease or condition.
3. It is not an orphan drug if any of the following persons or bodies has refused to approve it for use for the disease for a reason related to the medicine's safety:
   a. the Secretary;
   b. the Food and Drug Administration of the United States of America;
   c. the Medicines Control Agency of the United Kingdom;
   d. the Bureau of Pharmaceutical Assessment of Canada;
   e. the Medical Products Agency of Sweden;
   f. the Medicines Evaluation Board of the Netherlands;
   g. the European Agency for the Evaluation of Medicinal Products.
4. It is not an orphan drug if it has been registered for use for the disease or condition before 1 January 1998.
5. However, it may be registered before 1 January 1998 for another use or indication. [5]

Orphan Drug Designation

Under the regulation 16J of the Therapeutic Goods Regulation 1990 the decision is taken whether a medicine

qualifies the orphan status or not. The Registration application is filed then the designation application is submitted for requesting the assessment of the orphan drug eligibility criteria from the regulatory body TGA. As soon as the orphan designation is granted by the TGA then the application fee and the evaluation fees are waived. The orphan drug registration can be done through the process of the prescription medicines itself. The registration on the ARTG should be done separately as the orphan designation doesn't guarantee the registration in the (ARTG). [6]

Benefits of the orphan drug designation

i. The orphan drugs will be easily available in the market
ii. The total drug development cost can be reduced
iii. A transparent and consistent process for assessment against the orphan designation suitability criteria.

The drugs for the orphan drug designation shall have the same documents necessities as that of the other medicines or prescription medicines these will be evaluated by the TGA for its quality, safety and efficacy.

Eligibility of orphan drug designation

The following criteria should be fulfilled when the company applies for a designation application:

i. The orphan drug approval is granted in the following criteria:
ii. A formerly unregistered medicine
iii. The significant benefit criterion including all relevant criteria should be met by a major variation application, new dosage form, medicine with a new orphan indication for a previously registered medicine.

If the following criteria are fulfilled for any IVD, vaccines or drugs then the orphan drug designation is eligible according to16J of Therapeutic Goods Regulation.[7]

Table 1: Comparison of the standard orphan drug regulation 16J (3) and new dosage form medicine regulation 16J (4)

Application type	Standard orphan drug regulation 16j (3)	New dosage form medicine regulation 16j (4)
One indication	The request is for a single indication of a medicine only.	
Serious indication	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 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	
Orphan drug 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 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 Regulations were waived in relation to the medicine
Refusal to approve on grounds of safety	none of the following has refused to approve the medicine for the treatment, prevention or diagnosis of the condition for a reason relating to the medicine's safety: (i) the Secretary; (ii) the United States Food and Drug Administration; (iii) the European Medicines Agency; (iv) Health Canada; (v) the Medicines and Healthcare Products Regulatory Agency of the United Kingdom;	
Comparison with registered therapeutic goods	(i) no therapeutic goods that are intended to treat, prevent or diagnose the condition are included in the Register (except in the part of the Register for goods known as provisionally registered goods); or (ii) if one or more therapeutic goods that are intended to treat, prevent or diagnose the condition are included in the Register (except in the part of the Register for goods known as provisionally registered goods)—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.	

Orphan drug designation

The designation for a medicine should be specific to the:

· sponsor

· orphan indication for which designation was granted

· dosage form of the medicine.

Orphan designation cannot be transferred from one sponsor to another.

Orphan designation for multiple indications

The medicine with a single indication can only be applied. In case the company needs to apply for a medicine with more than one indication then the separate indication application has to be submitted for each orphan indication. In this regard the treatment, prevention or diagnosis will be considered as a distinct indication and it will be applied separately for each designation.

Supporting document requirements

The main body of the designation application should not exceed 30 pages if there are any supporting documents then it shall be added as the addons. The main body should contain the proof for the following steps to satisfy the eligibility criteria

a. Description of the orphan condition which includes the details of the same, proposal, and the therapeutic indication for the registration.
b. Justification shall be given for the life-threatening condition
c. The prevalence of the disease and the industry should give appropriate justification for financial lacunae.
d. The summary of the product development, it should also include the current regulatory status in Australia and in other countries and description about the medication if it's been refused in few of the regulatory agency.

The applicability and explanation as to why the orphan drug is required for the Australian population.

The attachments to be included are:

- Pivotal study summary
- Supportive proof on the clinical trial data and comparison studies
- Safety data from the preclinical and clinical setting
- Published paper related with additional summaries
- Various literature references and unpublished reports may be added
- Abbreviation list

Only applicable information shall be published and any outdated or irrelevant information shall not be published

Table 2: Contents of the designation application [7]:

Steps	Contents of the designation application
Step 1	The description of the medical condition should include the details of the disease, the proposed condition and the proposed orphan indication along with the therapeutic indication for the registration process and the medical plausibility should also be included.
Step 2	The nature of orphan condition as a life-threatening disease should be justified.
Step 3	The prevalence of the orphan condition among the population and the lack of the finances should be provided.
Step 4	The registered therapeutic goods should be compared for their diagnosis, prevention and treatment in Australia and justification should be provided for the same.
Step 5	Description should be provided for the development of the product, the present regulatory status in Australia and overseas.

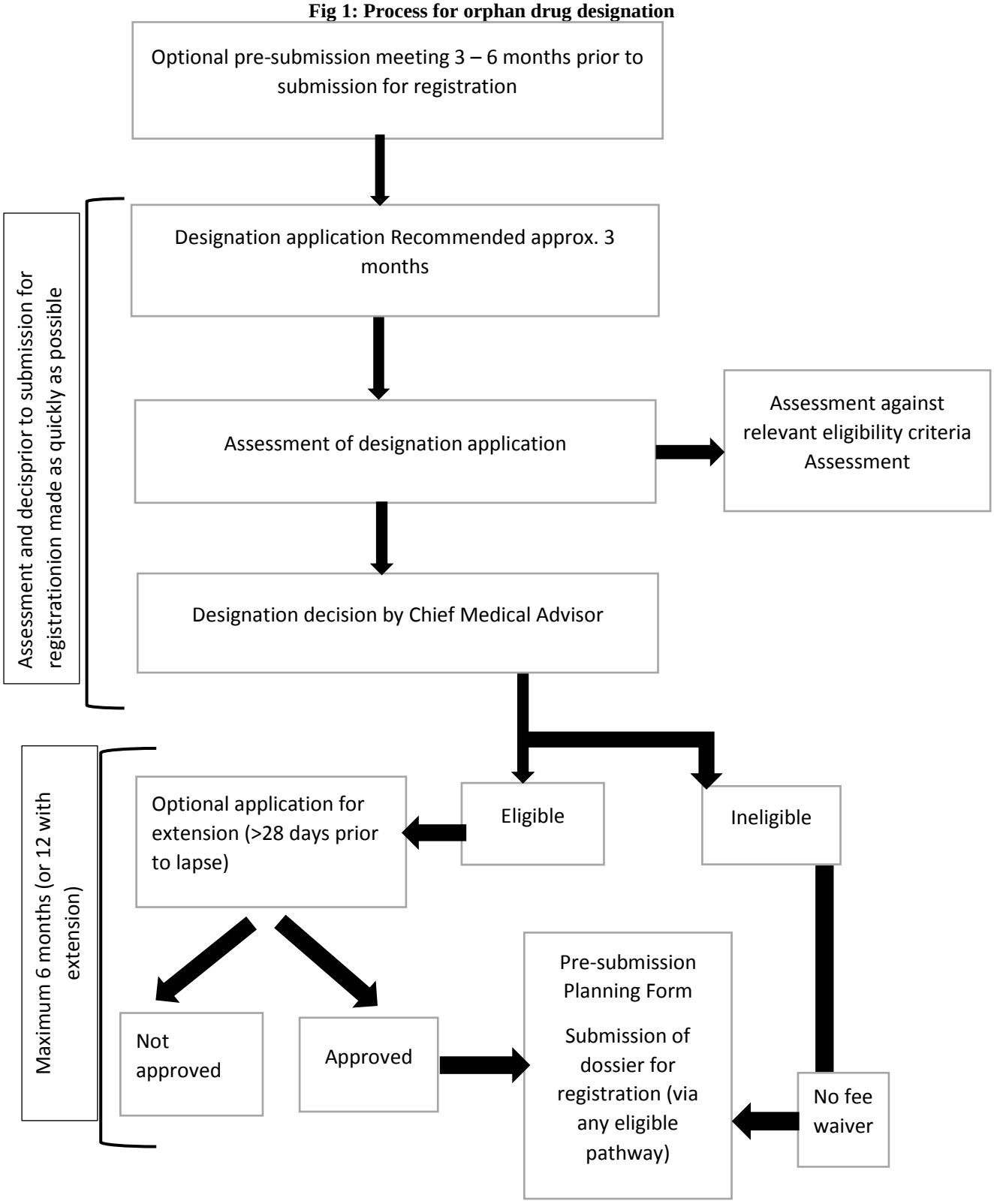
Table 3: Process of designation application and assessment

Stage 1	Pre submission meeting	Purpose: The prearranged designation application should be discussed with TGA Time: should occur 6 months prior to the date of submission of registration application
Stage 2	Access to TBS	Purpose: To obtain the Client Id number and Password to access TGA business services. Procedure: Documents required are: • a TGA client identification number (Client ID) • Password to access TGA Business Service Portal • Submitter access to TBS portal
Stage 3	Submission of designation application	Time: The designation application should be submitted three months before the date of lodging the registration submission. Eligibility: Under 16H (2) the designation should be submitted using the designation/determination application e-form which is an approved form, this form can be accessed through TBS account. The active ingredients should have an approved name: Once the active ingredient list is being recorded it should be checked whether each of the active ingredient has the approved terms as the following Australian approved name (AAN) Australian approved biological name (ABN) • In the application for orphan drug designation only approved ingredient names should be used.

		• In the approved list if the active ingredient is missing then a proposal is to be submitted to the TGA along with the orphan designation application. • The form AAN and ABN should be used to apply for the approved names. • The application form for the orphan drug designation should contain the proposed names in brackets it should also be mentioned that those names are been proposed. Fees for the orphan drug designation: The determination application fee should be paid if the submission is regarding the orphan drug designation application.
Stage 4	Assessment of the designation application	Purpose: Assess the designation application by TGA Contents of the application which will be checked are: • A completely filled form along with declaration • Administrative requirements should be met • Each and every eligibility criterion should be scientifically justified • The justification should be up to date • And it shall include all supporting data and references wherever required. Process of assessing the designation application: The designation application shall be reviewed against the eligibility criteria which is present in 16J (3) or (4) of the regulations, the main objective is to assess whether the criteria is met. Requests to the sponsor for additional information by TGA: Extra evidence may be requested by the TGA during the course of the assessment for which a timeframe may be given according to the case and its details, the usual time frame which is given is 5 working days. The time taken by the company may extend the overall assessment and the decision-making time frame. Withdrawal of the designation application: The company may withdraw the application before the notification of the TGA by sending an email to AET.Application.Entry.Team@health.gov.au And the email should contain • A statement for the withdrawal of the orphan drug application • The number of the designation application • The active ingredients name • The name of the sponsor • The proposed orphan indication for the designation
Stage 5	Notifying sponsors of the designation	After assessing the application for the eligibility criteria of the designation the medicine will be designated as an orphan drug. After the decision is made by the TGA they'll send an email (according to sub regulation 16J (6) and 16J (7)) The decision letter shall include • The name of sponsor of the medicine • The name of the medicine • Each active ingredient of the medicine to which the designation relates • The orphan indication • The dosage forms If the delegate decides to refuse to designate the medicine as orphan drug then the decision letter shall also include: • Reasons for the decision to refuse to designate the medicines as an orphan drug • Details of the appeal rights Method to request the designation decision; The requisition of the orphan designation can be done under the regulation 48. The appeal should be lodged within 90 days of the designation decision being issued. Publication of designation outcomes If the orphan drug designation is approved then the details of the eligible designation decision will be published in the website (Subregulation 16J (5)). • The publication shall include: • The name of the medicine • The sponsors name • The eligible orphan indication • The dosage form • The designation decision date and the lapsing date The designation decision shall be published as soon as the company is notified Period in which the designation is in force:

		The orphan drug designation comes into force when it is made and remains in force for six months (refer sub-regulation16K (1) of the Regulation) unless it is extended or revoked. Applying for extension of the orphan drug designation: If unable to lodge a submission for registration within the initial six-month period of validity then it is necessary to apply to TGA in writing for an extension of orphan drug designation only. The approved extensions shall be granted for further six months as set out in the sub-regulation 16L. The application for extension of orphan drug designation should be lodged in an approved form using the designation/determination extension application e-Form in the TGA business services at least 28 days before the designation lapse date. The application made less than 28 days before the designation lapse date will not be accepted for the assessment (sub regulation 16L(2)(b)) In the application form and supporting documents the following details are to be furnished: The reason for extension and justification as to whether the extension will allow to lodge a registration application within the extension period • Updated justification that there are no existing therapeutic goods for the diagnosis, prevention or treatment of the condition in question or • If such therapeutic goods existed then the medicine will bring improved efficacy, safety or a major contribution to patient care of those affected and • A current update on the approval status of the medicine by the regulatory agency as specified in regulation 16J (3) or (4) as applicable. The medicine may no longer be eligible if the application has been refused by one of the regulatory agencies due to the medicine safety • An update should be provided on any other aspects of the designation application that have changed since the original designation application • The orphan drug designation cannot be extended if the TGA has previously extended the designation (sub- regulation 16L(4)(a)) No fees for the applications to extend orphan drug designation. Assessment of the extension application: Additional clarification is required from the TGA throughout the assessment of the designation extension application. Notification of the Outcomes – Application for extension: • The outcomes of the application will be notified through email as soon as the decision is made by the TGA • The approved extension letters shall include details of the extended orphan drug designation period. • If the application for extension is not approved then the reasons will be stated. • Decisions regarding a refusal to extend an orphan drug designation can be appealed under the regulation 48. • Only one extension for one orphan drug designation. Revocation of the orphan drug designation: The TGA reserves the right to revoke the designation prior to the end of the designation period under Regulation 16M. Re-lodgement of lapsed designation: If the designation and its extensions have lapsed and the company needs the orphan drug waiver then a new designation application is to be submitted. The new designation application will be reassessed against the eligibility criteria. The reference numbers of previous designation application should be included for the new application for designation.
Stage 6	Submission of application for registration	The application for registration of the designated orphan drug can be submitted through any of the prescription medicines registration pathways. Waiver of the Registration Fees: To become eligible of waiving the registration fees related to orphan designation for the medicine, indication, dosage form and sponsor must be in force when the relevant fee is payable. The application fees are payable at the time of making an application for the registration and the evaluation fee is payable on the day on which the applicant is notified of the amount of the evaluation fee. Fees are payable if the orphan designation for the medicine has lapsed, or the application is outside the scope of the orphan designation. There is no requirement for an orphan drug designation to be renewed. A new orphan designation can be applied any time.[6]

Fig 1: Process for orphan drug designation



CONCLUSION

The patients suffering from the orphan diseases has same right to acquire medicine as the other patients who are suffering from a well-known disease. With this background the orphan drugs are in the special case as they are developed and marketed only because special incentives are being provided in case of TGA they provide waiver of registration and evaluation fee as soon as they are designated as orphan drug. The orphan drug designation is important for the industry to get the incentives and support from the stakeholders. This article discuss about the process for applying an orphan drug designation of a prescription medicine to receive a waiver of application and evaluation fee for registration on the Australian Register of Therapeutics Goods (ARTG)

REFERENCES

1) Van Weely S, Leufkenz HGM, Priority Medicines for Europe and the World "A Public Health Approach to Innovation" Background paper 6.19 Rare disease updated on 2004.
2) Zoran Nakov, Jasmina Tonic-Ribarska, SuzanaTrajkovic Jolevska. Orphan diseases, orphan drugs and orphan regulation in USA and EU. Journal of Pharmacy, 2016; 6(11), 5-10.
3) Orphan drugs program Discussion paper May 2015 by TGA
4) Orphan drugs fact sheet by rare voices Australia
5) Consultation: orphan drug program 2015 consultation outcomes and 2016 orphan drug program proposal by TGA version 1.1. October 2016
6) Orphan drug designation a step by step guide for prescription medicines version 1.1, August 2018 by TGA.
7) Orphan drug designation eligibility criteria including supporting documentation version 1.1, August 2018 by TGA.