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Review Article

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Regulatory Strategies for Orphan Drug Development in Canada – Australia

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Abstract

Canada, Australia have evaluated how their governments can facilitate the improvement of scientific merchandise to deal with uncommon issues. Each has hooked up programs and/or policies to help the improvement of merchandise to deal with unmet clinical wishes in small populations and to ensure their citizens get right of entry to such important medicines. Australia's software, initiated in 1998, changed into evolved in collaboration with the United States Food and Drug Administration to facilitate the alternate and evaluation of facts on orphan tablets. Canada's evaluation, posted in 1996, determined that a standalone orphan drug software became now not presently warranted, as present regulation and regulatory policies permit early get right of entry to critical medicinal merchandise. The incidences of such diseases were increasing at an extra pace than the speed with which drugs are researched and developed to treat such diseases. One of the fundamental motives is that the pharmaceutical enterprise is not very keen to research the improvement of orphan capsules as those capsules do no longer capture a larger market. This is the modern situation in-spite of the various incentives furnished in the orphan drug act. However, in this article, we've tried to focus on present regulatory framework, Current principles of rare sickness, Regulatory Challenges for Rare Disease Drug Development, Regulatory Integrated approach for the improvement and approval of orphan drugs in Canada & Australia.

Keywords: Regulations of Orphan Drugs, Regulatory Challenges, Regulatory Orphan Drug Life Cycle. Canada, Australia

Introduction

The United States Orphan Drug Act have become law in 1983, and in January 2000, the European Communities law on orphan medicinal merchandise came into force. Between the enactment of those primary pieces of legislation within the United States, Europe, regulations and programs to inspire the improvement of merchandise to treat rare problems have been put in area in different fundamental regions United States application and needs to publicly acknowledge the big assist obtained of the world.

Canadian Context

Canadian History In the absence of an orphan drug regulatory framework, Canadians can access such orphan drugs through the Special Access Program of Health Canada, clinical trials or as new drugs receiving a Notice of Compliance under Part C, Section 8 of the Food and Drug Regulations. Symptoms of neurofibromatosis, incomplete osteogenesis, chondrodysplasia or Rett syndrome in Canada, Huntington disease, Crohn disease, Charcot-Marie-Tooth disease, lateral amyotrophy, Kaposi's sarcoma or thyroid cancer.

While these approaches have worked in the past, they are restricted in both providing access to orphan drugs and gathering and sharing information as they have not been designed to address the unique challenges of rare diseases.

Orphan Drugs under the Canadian Food and Drugs Act

- Proposal is to create a legislative system that will provide Canadians with access to orphan drugs without sacrificing patient safety, resolving the unique challenges of monitoring small populations of patients and aligning Canadian regulatory practices with those of international partners.
- The plan would provide a regulatory scheme that would transparently define what an orphan drug is and control the benefits, drawbacks and risks by considering the existence, planned use and distribution of orphan drugs throughout the life cycle.
- The life-cycle approach would provide sufficient regulatory oversight from classification and development of clinical trials to post-approval monitoring authorisation. It would provide a better opportunity to receive both expert advice and patient insight on the nature of the disease to provide a greater context for regulatory decisions. This will be achieved by providing a broader range of tools to gather and resolve new information, including the ability to intervene through a change of mark, re-evaluation, stop-sale, termination, and cancelation of an approval.
- Comprehensive approach would step away from the current static, timely regulatory framework found in Food and Drug Re, Part C, Division 8 From the Food and Drug Regulations to a

more structured, flexible and versatile collection of measures to better serve the needs of patients while maintaining strong health monitoring. This is critical for small vulnerable populations that have no other choices at their fingertips to relieve their suffering.
- As an early deliverable in the Health Products and Nutrition Regulatory Roadmap, the life-cycle principles first adopted in this regulatory framework would guide all other attempts to modernize the following drugs and medical devices.

• Definition of orphan drugs – According to the Australian Regulation (TGA),

- Definition of orphan drugs – According to the Australian Regulation (TGA), the word "orphan drugs" applies to medicines, vaccines or products that identify, prevent or treat people with rare diseases (i.e. diseases occurring in less than 1 in 2000 people in Australia). Examples of rare disease: pemphigus vulgaris, cystic fibrosis (CF)
- Chronic myelogenous leukaemia, Haemophilia.
- As a result, pharmaceutical companies typically do not benefit from orphan drugs. The shortage of drugs to treat rare diseases means the diagnosis and treatment of people with rare diseases is refused. Patients with rare diseases have the same quality, impact and protection right to medications as patients with more common diseases. The Orphan Drug was created by the Therapeutic Goods Administration (TGA).
- The Australian Orphan Drug Program launched to 1998. The program's aim is to encourage Australia's accessibility of orphan drugs. To order to receive approval from the TGA, the drug must go through an assessment process before a drug can be made available in Australia. In terms of safety, reliability and clinical efficacy (performance), the evaluation process looks at the drug. Except when the medication is an orphan drug, there are costs involved in having the TGA test products, in which case there is no cost to the review. It offers a major financial benefit for pharmaceutical companies, allowing them to be approved by the TGA for orphan drugs.
- The pharmaceutical company that developed the medication will prove to the Orphan Drug Program that the drug is not commercially viable for such a small patient group to be declared an orphan drug in Australia. The Orphan Drug Program often reduces the time it usually takes for a drug to be tested by the TGA.
- Refer to the website for a list of orphan drugs available in Australia: http:/www.tga.gov.au/industry/pm-orphan-drugs.htm Once a drug is classified as an orphan drug, it is easier for the drug to become accessible and can be obtained under certain conditions through the Life Saving Drugs Program.

- **Current principles of rare disease in CANADA**
- **Rare Disease Principle 1:** Rare disease patients are entitled to equality in access to health care, which may result in inequity in the calculation of therapy quality.
- **Rare Disease Principle 2:** Fair access should consider public preference (added value) for treatment of patients with serious and debilitating conditions where good alternatives are not available
- **Rare Disease Principle 3:** Regulatory approval of a rare disease drug must consider special clinical trials designed to accommodate rare disease patients. For example, CTs identified by:
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- Rare Disease Principle 3: Regulatory approval of a rare disease drug must consider special clinical trials designed to accommodate rare disease patients. For example, CTs identified by:

- **Current principles of rare disease in AUSTRALIA**
- **Orphan criterion: medical plausibility and biomarkers:** endorse the preservation of the principle of medical plausibility; the procedure is consistent with the EU criteria, where the distinct condition is defined in terms of specific characteristics, e.g. pathophysiological, histopathological, and clinical.
- **Orphan Criterion: No current treatment or substantial advantage over established care:** Sponsors of Orphan Drugs are required to demonstrate that the medication meets an unmet medical need or will provide a significant benefit over existing treatment. TGA's acceptance of overseas designations by equivalent overseas regulators (CORs) could be a basic' recognition / ado 'the ' recognition ' of overseas COR designations often refers to designations where significant benefits are to be identified over existing therapies (Australian standard of care), as both the EMA and the US FDA have similar criteria. Nevertheless, the proposal to require the TGA's Principal Medical Advisor to receive independent expert advice (including from the Medicines Advisory Committee) should be reserved in exceptional circumstances only where, for instance, an Overseas Regulator has NOT approved an Orphan Drug Designation or clinical practice is different from that evaluated by the COR. It could be inferred that this was the recommendation's intention; however, this ' pathway ' was not outlined in the Consultation Paper, including the effect on evaluation times, especially in view of the proposed tight pre-submission deadline.
- **Point of consultation: pediatric populations are diagnosed in infancy and approx.:** as the rarest diseases. Thirty percent of children with rare diseases will die before the age of five with TGA, continue to promote access, reduce the use of labels and improve the collection of data in our most vulnerable small patient population Current

Challenges for Rare Disease Drug Development in CANADA

Rare diseases are hard to diagnose because of the small population affected and drugs used to treat them are difficult to study. It means that the regulator will treat these drugs ' regulation in a versatile way, taking into account the limited information that may be available and the need to obtain more once the drug is on the market.

- Challenges for orphan drugs used to treat small, vulnerable patient populations.
- Orphan drug classification (including common application process)
- Scientific and medical treatment guidance
- Increased open exchange of data
- Post-market authorisation compliance responsibilities
- Drug development opportunities including market exclusivity, fee waiver, priority request review

Challenges for Rare Disease Drug Development in Australia

- Plan for Rare Diseases of the Australian Government. Ultra-rare/ rare diseases share many of the "new victims" or "targeted therapies" challenges, but they face additional challenges.
- A general lack of understanding of disease pathogenesis and pathophysiology, and a shortage of health care professionals (globally) encountered in their diagnosis and management, lead to a significant delay in the timely and effective diagnosis and management of the disease (as opposed to focused, easily diagnosed biomarker / diagnostic treatments).

Regulatory Frame Work Of Orphan Drugs In Canada

Many current provisions of the Food and Drug Regulations will be used to regulate orphan drugs, including for:

- Clinical trials (Part C, Division 5, with possible exceptions)
- Company licensing and sound business practices (Part C, Divisions 1A and 2, with potential exceptions) '
- Exclusivity of the market (Part C, Division 8)

Orphan Drug Designation

Designation is a new step for Health Canada to take in a drug's regulatory life cycle Orphan Drug Designation is given for medical drugs intended for the diagnosis, prevention or treatment of a ' life'—threatening or permanently disabling that affects no more than five out of 10,000 people in Canada.

Health Canada aims to include guidance on research and medical guidelines, priority review, fee cuts for small to medium-sized businesses, and access to the current eight-year and six-month market exclusivity for new medicines.

Market Authorization Application

License criteria for orphan drugs will be identical to the Food and Drug Regulations currently in place. Significant new provision for transparency would include the condition for reporting that all clinical trials have been registered in a publicly accessible database in compliance with international standards. Providing a post-market plan to support the ongoing evaluation of the drug-related benefits, risks and challenges would improve the management of the life cycle (see Post-Market Strategy below). Priority review, like the current policy of Health Canada, will be granted for applications for orphan drug market authorization.

Orphan Drugs Market Authorization

A sales authorization is an authorization for marketing an orphan drug. While issuing individual Notices of Compliance, for each orphan drug, a single market approval would be given and could be updated, reassessed, suspended or cancelled. Regulatory guidelines will promote the public's accountability of an orphan drug market authorisation and include accessibility and openness. Publishing adverse decisions and the rationale for such decisions is essential for orphan drugs in situations where the use of an existing re-purposed drug on the market could continue off-label In this circumstance it is important to relay this information to the public and health professionals to prevent harm.

Post-Market Authorization Plans

As part of the Market Authorization, a plan will be required to support ongoing assessment and management of the drug-related benefits, harms and uncertainties and their use. It builds on current practices at Health Canada and around the world whereby companies provided the regulator with post-market plans for review at the time of request, including risk management plans and pharmacovigilance plans. Specific criteria for post-market preparation have recently been introduced in the Extraordinary Use New Drugs Regulation (EUND, see C.08.002.01(2)(b)(ix)). Getting such plans as a regulatory requirement allows better monitoring and re-evaluation once the drugs are on the market. Flexibility in how and in what way the application data is provided to Health Canada needs to allow for various formats such as those currently available in the US and EU. This will also require joint assessment projects with international partners to add efficiencies and focus expertise to the process.

Technical Description of the Proposed Regulatory Framework

A. General: Description and regulation to provide a regulatory framework for orphan drugs, a new Division would be established under Part C of the Food and Drug Regulations.

The regulatory framework will apply to orphan drugs for human use and include requirements concerning:

- Designation of orphan drugs
- Regulatory advice
- Expert and patient advice
- Industry authorisation
- Post-market authorisation responsibilities and capabilities

B. Orphan Drug Designation

a. Application for the designation of an orphan drug A sponsor may apply for the designation of an orphan drug. The sponsor must sign and date the application and include the following information:
b. The sponsor's name, address and telephone number and, where appropriate, the sponsor's fax and e-mail address and the sponsor's representative in Canada for a foreign sponsor;
c. If available, data on the drug's manufacturer(s) if the sponsor is not manufacturing the drug;
d. The drug's therapeutic components;
e. The sign proposed;
f. Sufficient data to show fulfilment of requirements under the concept of orphan drugs;

A review of the drug development stage, including the anticipated indications; and A review of the legal status of the drug in Canada and abroad, including existing research uses, past product authorizations, orphan drug classification status, and any regulatory actions, where applicable

Request for Additional Information

If the request lacks information or includes incorrect or incomplete information, the Minister may application that additional information be given by a sponsor within the time specified by the Minister.

If the sponsor fails to provide a response by the date specified in the application, the Minister would be able to consider the petition to be withdrawn unless the sponsor has sought an extension and the Minister has accepted.

Issuance of an orphan drug designation: If the requirements under the orphan drug concept were met, the Minister would be required to issue an orphan drug designation with respect to a drug.

Transparency: A registry of orphan drug designations should be maintained and made available to the public by the Minister.

C. Regulatory Advice: A person may submit a request for written regulatory advice at any time during the drug development process, which can only be changed through a modification process, in order to reach agreement on the type and amount of information required to demonstrate the benefits and harms associated with the use of an orphan.

The minister may change the regulatory advice if:

a. It is considered necessary to do so by both the Minister and the person who provided the regulatory advice; or
b. The type and amount of information identified in the regulatory advice is no longer sufficient for the Minister to assess the benefits and harms associated with the use of the orphan drug.

D. Expert and Patient Advice: Minister would be required to give a supporter, business authorization applicant or owner an opportunity to make representations when the Minister has received advice from experts or patient representatives, where appropriate, before:

a. Deciding to grant, deny or cancel the approval of an orphan drug;
b. To provide regulatory advice on an orphan drug;
c. Make a decision to issue, modify, refuse to submit or modify, suspend or cancel an orphan drug market authorization; or
d. Making a decision to maintain, modify or suspend a market authorisation for an orphan drug subject to re-evaluation

E.Clinical Trials: Orphan medicines to be used for clinical trials would be subject to the Food and Drug Regulations, Part C, Section 5, with possible minor modifications.

F. Legal authorisation for an orphan drug legal authorisation: An orphan drug issued under this regulatory framework would be excluded from section C.01.014 and subsection C.08.002 (1) of the Food and Drug Regulations. An individual can applies for an orphan drug to be approved on the market. The application must include the following information:

G.Changes to a market authorization: Changes to a market authorization requiring the submission of a request for amendment the selling of an orphan drug pursuant to a change requiring a market authorization owner to submit a request for amendment would be prohibited.

a. The owner of the business authorization would be required to submit an application for amendment including the details provided
b. Any shift in information that supports an orphan drug where that change has the potential to significantly change the advantages, risks and uncertainties associated with orphan drug use;
c. Any change to the market approved plan; e. Changes in any market authorization administrative information such as the market authorization holder's Name or address;

Review of an application to amend a market authorisation Modification of a market authorisation Modification of a market authorisation requiring notice

H. Changes to the brand name of the orphan drug market: authorization holder's obligations the requirements of an orphan drug market authorization which would apply to all market authorizations under this new division would be laid down as follows and would allow a market authorization holder to:

Labeling and packaging
Good manufacturing practices
Reporting of serious adverse drug reactions
Implementation and maintenance of the market authorized plan
Annual notification changes in regulatory status in other countries
Maintenance of records

I. Post-market Authorization Abilities

Ability of the Minister to request information
Ability of the Minister to allow a market authorization holder to compile information Ability of the Minister to require a change in the tag or packaging of an orphan drug Ability of the Minister to perform an orphan drug re-evaluation
Ability of the Minister to guide an individual to stop the sale of an orphan drug

J. Market exclusivity

Existing data privacy regulations pursuant to section C.08.004.1 of the Food and Drug Regulations and the conditions of the Patented Medicines Regulations (Notice of Compliance) will extend to market authorisations issued to orphan drugs, including certain amendments.

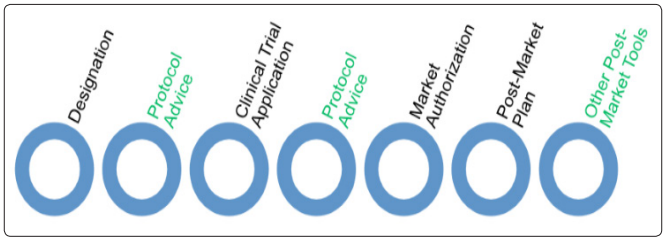


Figure 19: Canada Orphan Drug Life Cycle

Regulatory Frame Work of Orphan Drugs in Australia

Orphan drug designation: Classification is a formal process that enables us to make a decision on whether the medication is suitable for orphan drug classification under Regulation 16J of the Therapeutic Goods Regulations 1990 (the Regulations).

The application for classification precedes the application for registration and is the formal request made using a defined form requesting review against the applicable eligibility criteria and a TGA decision.

License and review fees are suspended for applicants for prescription medicine registration when an orphan designation is in place (see designation period).

You may apply for an orphan drug registry through any prescription medicine registration process available, according to the criteria for that registration process. An orphan drug status does not guarantee that the Australian Therapeutic Goods Registry (ARTG) is registered.

Eligibility requirements: The orphan drug program eligibility criteria are laid down in Regulation 16J of the Regulations

Orphan drug designation may be granted for:

- A previously unregistered medicine
- A new orphan medicine already registered, a new dosage type medicine or a major modification request which meets all relevant criteria including a significant benefit criterion

Eligibility criteria for the orphan drug designation: An orphan medication may be eligible for a medicine, like vaccines or in vivo diagnostic agents, if all orphan requirements in the table below are met (Regulation 16J of the Therapeutic Goods Regulations 1990 (the Regulations)). A process to scan for orphan status for new dosage type drugs is required in addition to the standard orphan classification. Eligibility for a new form of dosage

Technical Description of the Proposed Regulatory Framework for Orphan Drug designation

- Promoter
- Orphan indication for which recognition has been given
- Drug dosage type., It is not possible to transfer the orphan designation from one donor to another.

Several signs Orphan label

Just one sign of the drug can be added. For more than one indication, if you are seeking orphan drug designation, separate designation applications for each orphan indication must be submitted. Treatment' and' prevention' or' diagnosis' of the same disease are considered separate signs in this regard and should be the focus of separate development applications

Content of the application for designation: We will determine on a case-by-case basis the validity of the justifications. The extent to which criteria are met will be assessed as part of the routine designation process, considering current information on the date of the designation lodgement. The sponsor may withdraw an application for designation prior to the decision. After a decision, the classification may be withdrawn if the TGA is satisfied that any orphan designation requirement is no longer met (Regulation 16 M). During the time of their validity, we will not regularly review classification decisions, but may do so in exceptional circumstances.

Step 1: Provide a summary of the condition in this section

- Description of the orphan disease: the application for classification must provide description of the disorder to be diagnosed, avoided or treated by the drug. Information will contain:
- A concise definition of the disease or condition involved
- Signs and symptoms descriptions
- Refer to international disease classification systems such as the International Classification of Diseases (ICD) of the WHO or other well-recognized classification systems (e.g., tumour classification of the central nervous system of the WHO).
- Refer to international disease classification systems such as the International Classification of Diseases (ICD) of the WHO or other well-recognized classification systems (e.g., tumour classification of the central nervous system of the WHO).
- The suggested sign of an orphan
- Proposed orphan indication at registration and therapeutic indication
- Plausibility of medicine
- Biomarkers are used to replace a condition

Step 2: To explain the life-threatening or seriously disabling nature of the condition: it is necessary to justify the seriousness of the illness, i.e. its seriously debilitating or life-threatening nature, on the basis of reliable and quantifiable clinical or epidemiological information.

Justify the: Life-threatening features of the mortality and life expectancy-based disease

- Sadly, crippling existence of morbidity-based illness over time and its impacts on daily functioning of patients.
- Extreme weakening or catastrophic outcome should be a key feature of the target disease and therapeutic indication, i.e. affecting a significant portion of the target population.

Step 3: Include either the condition's prevalence or a reason for lack of financial viability

- *Prevalence of the orphan syndrome suggested*
- *Calculation of the prevalence of diagnosis drugs*
- *Calculations of prevalence of therapeutic or preventive drugs*
- *Prevalence and prevalence of Australia's condition*
- *Viability of finances*
- *Subsidies and tax incentives*

Step 4: Contrast for diagnosis, prevention or treatment of licensed therapeutic products in Australia

- *Therapeutic services registered*
- You will update the proposed indication in Australia with licensed medicinal products for diagnosis, prevention or rehabilitation and provide:
- Details of any registered therapeutic products for diagnosis, prevention or treatment of this indication (Table of Trade Names, ARTG entry holder, and registered indication)
- Either a rationale that demonstrates significant advantages over current pharmaceutical products

OR

A statement that, in compliance with ARTG entries on the date of classification lodgement, there are no licensed medicinal products in Australia.

- Justification of a significant benefit
- One of the following should be provided as a justification for a significant benefit: Increased efficacy-for the entire population impacted by the new orphan condition
- Increased safety — a better safety profile or tolerability for the entire population impacted by the proposed orphanage

Major contribution to patient care — ease of use in a particular group of patients or self-administration, e.g. where new treatment allows for outpatient treatment rather than hospital treatment only or has a significant impact on ease of use and decreases the cost of treatment;

Step 5: Phase of development overview Description of product development

The current development status of the proposed orphan medication, clinical examination and specifics of the proposed application dossier for registration should be listed briefly. In other conditions or other patient classes, you should provide information on any potential changes and registrations. It is not appropriate to provide the full study reports of non-clinical and clinical studies

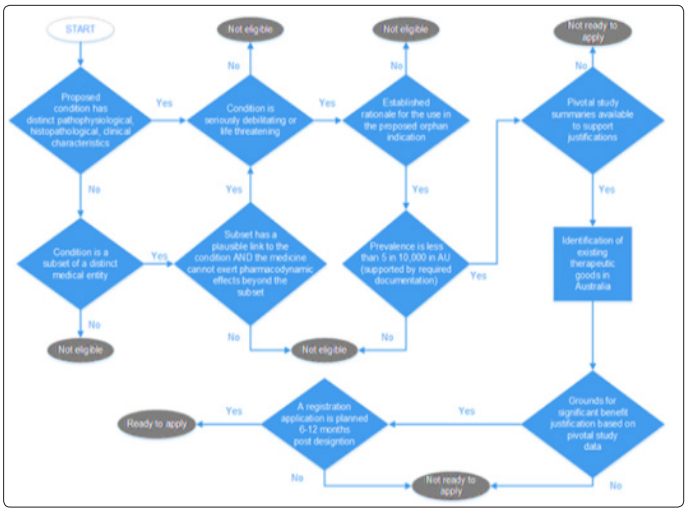
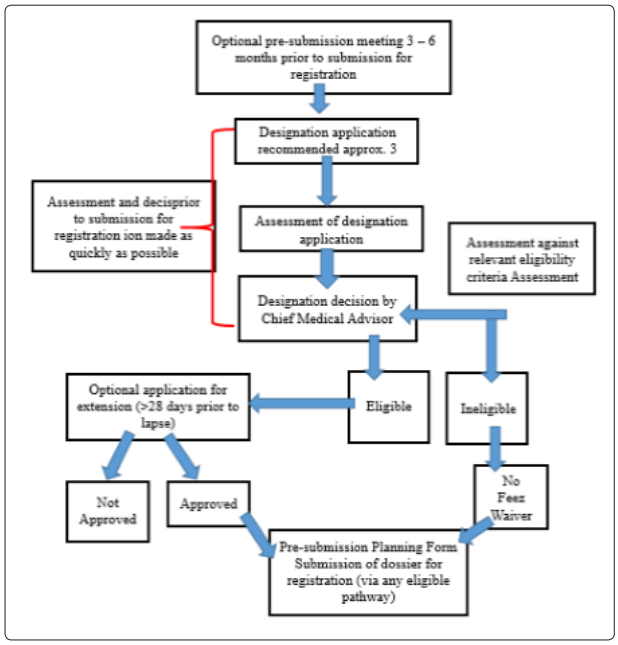


Figure 21: Australia Orphan Drug Life Cycle

Orphan Drug Designation in Australia



Integrated approach for the development and approval of orphan drugs in CANADA

Goal #1: Early detection and preventive improvement:

1. Adopt a new born screening regional approach:
2. Early warning and prevention programs are introduced across Canada

Goal # 2: prompt, equitable and well-informed care:

3. Improve health care providers ' training and capability in connection with rare diseases, including genetic counsellors
4. Tackle disparities in systems of social care for people with serious disorders
5. Create regional policies to ensure adequate housing for workplace people with rare diseases
6. Provide the same compensation for health services (e.g., physiotherapy) for people with rare diseases as for people with more common diseases
7. Establish centres of excellence on rare diseases to produce and promote research and patient treatment, develop and implement recommendations for clinical practice, create and provide general healthcare practitioners and the public with professional and patient education, and develop and support comprehensive diagnostic, medical and educational services, such as telemedicine or satellite specialized services
8. Consider the creation of a national registry for all rare diseases and endorse new and existing registries for diseases
9. For diseases where advanced facilities and online medical networks may not be feasible, make sure that patients with rare diseases are better integrated into existing Complex Care Facilities or Medical Homes
10. Take measures to promote linkages between administrative healthcare databases across the country to support the delivery of healthcare services to rare disease patients.

Goal #3: Improving the support of the community:

11. Rare disease-specific patient groups, as well as CORD and RQMO, should be adequately funded to fulfil their goals, including involvement in research projects, awareness transfer, policy development, training, interaction and patient care programs.
12. Boost capital to maximize Orphan's utility for all stakeholders

Goal #4: Providing safe access to treatments promising

13. That's right. Implement an orphan drug regulatory framework
14. That's right. Implement an orphan drug regulatory framework
15. Improve and formalize the role of patients in the market authorisation process and the generation of post-market evidence and provide resources to support rare disease patient groups' participation in this process
16. Establish a separate, more robust system of assessment of health technology adapted to the specific characteristics of orphan drugs
17. Increased support to assist groups of patients with rare diseases in the conduct of medical technology reviews, including the preparation for patient feedback
18. Establish a clear funding strategy for patient access to orphan drugs in a timely and equitable manner

Goal #5: Promotion of ground-breaking work

19. Provide committed and expanded funding for research into rare diseases and the Rare Disease Centres of Excellence
20. Establish a new Canadian Consortium for Rare Diseases to help coordinate a national agenda for rare disease research and centres of excellence on rare diseases.

Integrated approach for the development and approval of orphan drugs in AUSTRALIA

- Disease prevalence (almost 2000 patients) reflects a small population
- Converted to Australian requirements based on the United States system
- The method of Designation and evaluation is the same as in the United States
- Review charges waived
- Material adjustment fees and annual fees apply (low volume reduction)
- No specified time of exclusivity on the market, but products of the same active ingredient

- If clinical superiority is shown, the exclusivity of the market will be investigated in the system analysis (after approval of 10 products)

a. Orphan Drugs definition

- Relevant legislation:
- *Therapeutic Goods Act 1989, Part 3B Section 16H Orphan Drug*
- (3) A medicine, vaccine or in vivo diagnostic agent is an orphan drug if it complies with this regulation.
- (4) It: (c) Must be intended to treat, prevent or diagnose a rare disease
- or
- (d) Must not be commercially viable to supply to treat, prevent or diagnose another disease of condition.

b. Patient Threshold

Relevant legislation:
Therapeutic Goods Act 1989, Part 1: Preliminary, Section 2
A rare disease is a disease, or condition, likely to affect not more than 2,000 individuals in Australia at any time. An orphan drug is defined by the TGA definition of a rare disease (as per *Therapeutic Goods Act 1989*, Part 1: Preliminary, Section 2 '*at any one point there are no more than 2,000 people with the disease in Australia*').

Charging Model

- Relevant legislation:
- *Therapeutic Goods Act 1989, Division 2 – Fees and costs, Regulation 45*
- (12) The Secretary must waive the following fees:
- (a) a fee that would have been payable, but for this sub regulation, for applying to the Secretary under sub regulation 16I(1) to have a medicine designated as an orphan drug;
- (b) a fee that would have been payable, but for this sub regulation, for the Secretary considering the application under regulation 16J;

Requirements for the registration of Orphan drug product in CANADA

The application must contain the following information:
Following information:

a. The name, address and telephone number, and if applicable, the facsimile number and electronic mail address of the applicant and the applicant's representative in Canada in the case of a foreign applicant;
b. A statement signed and dated by the applicant's senior executive officer in Canada and senior medical or scientific officer, that all information contained in, or referenced by, the application is complete and accurate and is not false or misleading;
c. A copy of the Canadian orphan drug designation;
d. Information as to the designation and regulatory status in other countries;
e. The brand name under which the orphan drug is proposed to be sold;
f. A quantitative list of the medicinal and non-medicinal ingredients contained in the orphan drug, by their proper names and common names;
g. The recommended conditions of use for the orphan drug, including:
i. its recommended use or purpose;
ii. its dosage form and strength;
iii. its recommended route of administration;
iv. its recommended dose;
v. Information about its harms, including any cautions, warnings, contra-indications or known adverse reactions associated with its use.

a. Information relating to the benefits, harms and uncertainties of the orphan drug when it is used in accordance with the recommended conditions of use, including a plan to support the ongoing assessment and management of the benefits, harms and uncertainties associated with the use of the orphan drug. The plan must be proportionate to the benefits, harms and uncertainties of the orphan drug and must contain the following elements:

i. *Drug information: Medicinal ingredient(s), brand name(s), drug class as described in the label, indications, dosage form, strength(s), applicant's name & address*
ii. Contact information: *Name and contact information for the person(s) responsible for the plan*
iii. **Summary of the benefits, harms and uncertainties associated with the use of the orphan drug:** The summary is meant to form the basis for the activities and interventions described *in paragraphs iv. and v. below. For example, the summary would include a description of the identified harms, potential harms and uncertainties that may have an impact on the assessment of the benefits, harms and uncertainties associated with the use of the orphan drug.*
iv. **Detailed description of activities to monitor the benefits, harms and uncertainties associated with the use of the orphan drug once on the market and detect any change, including the assessment of the effectiveness of those activities.:**

- *The activities would be proportionate to the benefits, harms and uncertainties of the orphan drug. For example, they can include:*
- *Routine vigilance activities such as standard ADR reporting (as required by the regulations); Additional activities where routine vigilance activities are not sufficient for monitoring the benefits and harms and resolving uncertainties.*
- *Additional activities can include specific requirements for monitoring and reporting of ADRs (which differ from standard regulatory requirements) or post-authorization studies (both clinical or quality studies)*

v. **Detailed description of interventions designed to optimize benefits, prevent or minimize harms and clarify uncertainties associated with the use of the orphan drug, including the assessment of the effectiveness of those interventions.**

- *The interventions would be proportionate to the benefits, harms and uncertainties of the orphan drug. For example, they can include: Routine interventions (e.g. labelling as required by the regulations);*
- *Additional interventions, when essential for the safe and effective use of the orphan drug, including communications which aim to augment the information in the label (e.g. communications to healthcare professionals or patients/ consumers, educational materials), controlled distribution systems (including restrictions)*

vi. Timetable for the submission of assessments of the effectiveness of the activities and interventions, including reporting schedule • *the timetable would identify the frequency of assessment of the plan to ensure that the benefits of the drug continue to outweigh the harms*.

vii. Summary of the plan: *The summary should contain the key elements of the plan that will be made available to the public.*

h. Documentation that all clinical trial evidence was collected in accordance with accepted ethical standards, regardless of where the trials were conducted.
i. Documentation that all clinical trials performed or sponsored by the applicant were publically registered no later than 21 days after the first subject is enrolled, in accordance with internationally accepted standards.
j. Mock-ups of labels and packages to be used in conjunction with the orphan drug.
k. The names and addresses of the manufacturers of each of the ingredients of the orphan drug and the names and addresses of the manufacturers of the orphan drug in the dosage form in which it is proposed to be sold.

l. A detailed description of the orphan drug and of its ingredients that contains the following information:

i. A statement of all properties and qualities of the ingredients that are relevant to the manufacture and use of the orphan drug, including the identity, potency and purity of the ingredients,
ii. A detailed description of the methods used for testing and examining the ingredients; and,
iii. A statement of the tolerances associated with the properties and qualities of the ingredients.

m. A description of the plant and equipment to be used in the manufacture, preparation and packaging of the orphan drug.
n. Details of the method of manufacture and the controls to be used in the manufacture, preparation and packaging of the orphan drug.
o. Details of the tests to be applied to control the potency, purity, stability and safety of the orphan drug.
p. Evidence that all test batches of the orphan drug used in any studies conducted in connection with the application for market authorization were manufactured and controlled in a manner that is representative of market production.

Requirements for the registration of Orphan drug products in Australia: the main body of your designation application should be no more than 30 pages. Additional supporting documentation can be included as attachments.

The main body should address:

- steps 1 to 5 of this guidance document including a description of the condition and justifications for all relevant eligibility criteria
- where applicable, a justification as to why a new dosage form may be necessary for the Australian population

Attachments can include:

- summaries of pivotal studies, e.g. the study synopsis included as part of the body of the clinical study report, or where study synopses are not available, a summary of the study with sufficient detail to inform assessment (a full module 2 summary is not required); do not submit full study reports
- Supporting evidence based on clinical trial data. Comparator studies are expected to be generated (pivotal study reports)
- summaries of any available other important safety data obtained in the preclinical and clinical setting (both in the orphan condition and in other conditions and/or how safety information from other formulations may be applicable)
- where published papers are highly relevant, the full text of such literature (including supplementary appendices)
- other forms of literature references or unpublished reports and expert statements may also be used in addition to the pivotal study summaries but would be considered low level evidence
- an abbreviation lists
- It is expected that any supporting information is currently relevant. Information that is out of date or obsolete must not be submitted
- Applications for designation which are based on the financial viability of the medicine are considered under financial viability.

The Australian specific annex should include:

- updated prevalence or justification why EMA prevalence applies
- financial viability for Australia
- comparison against ARTG registered therapeutic goods/ justification of significant benefit
- details of the regulatory status in Australia and overseas
- pivotal study summaries

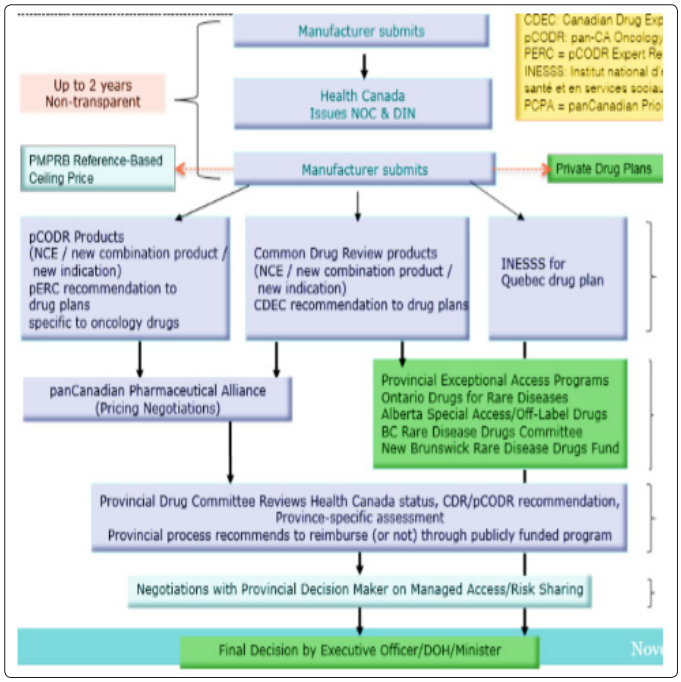


Figure 26: Orphan Drug Review Process in Canada

Table 14: List of Canada – Health Canada Approved Orphan Drugs

Generic Name	Company	Designation	Indication
Pasireotide	Novartis Pharmaceuticals Corporation	Treatment of Cushing's disease	SIGNIFOR® LAR is indicated for the treatment of patients with Cushing"s disease
Pasireotide	Novartis Pharmaceuticals Corporation	Treatment of Cushing's disease	SIGNIFOR² LAR is indicated for the treatment of patients with Cushing"s disease

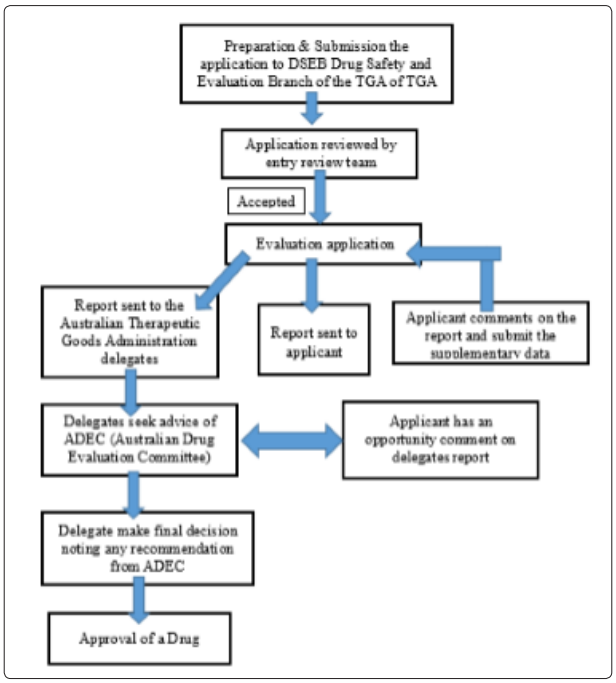


Figure 27: Orphan Drug Review Process in AUSTRALIA

Table 15: List of Australia –TGA Approved Orphan Drugs

Drug	Disease/Condition	Date of Designation	Date of registration in Australia
Adalimumab	For the treatment of active Crohn's Disease defined as a Paediatric Crohn's Disease	02/11/2012	24/6/2014
Drisapersen	For the treatment of patients with Duchenne muscular dystrophy (DMD)	10/12/2013	Yet to be registered

Refernces

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