

Office of Legislative and Regulatory
Modernization

**Initial Draft
Discussion
Document for A
Canadian
Orphan Drug
Regulatory
Framework**

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Preamble

The objective of this document is to provide context and policy intent for the proposed orphan drug regulatory framework including the details of the proposal.

Background

What is a rare disease?

A rare disease is a life-threatening, seriously debilitating, or serious and chronic condition affecting a relatively small number of patients (less than 1 in 2,000). Worldwide approximately 6,000 to 8,000 rare diseases have been identified. More than 80% of rare diseases are genetically-based with the remainder being a result of viral or bacterial infection or environment causes. More than half of rare diseases start in early childhood and are degenerative and life-threatening in nature. In Canada, 1 out of 12 Canadians is affected by a rare disease.

What is an orphan drug?

An orphan drug is a pharmaceutical or a biological drug that has been designated and developed to treat a rare disease. Since 1983 the US has brought in over 408 orphan drugs to the US market. This represents only a small percentage of those drugs that have been designated as orphan but have not reached the US market place. In the last two decades a steady average of 14 new orphan drugs has been approved annually in the US.

Unique Challenges of Regulating Drugs for Rare Diseases

Because of the small population affected, rare diseases are complex to diagnose and drugs used to treat them are difficult to study. This means that the regulator has to approach the approval of these drugs in a flexible manner considering the limited information that may be available and the need to retrieve more once the drug is on the market.

International Context

Most developed countries have regulatory frameworks that support access to clinical trials and drugs for rare diseases. These frameworks are specifically tailored to the evidentiary challenges for orphan drugs used to treat small, vulnerable patient populations.

Common features found in international frameworks include:

- Orphan drug designation (including common application process)
- Scientific and clinical protocol advice
- Better information sharing to support transparency
- Post-market authorization monitoring obligations

- Incentives for drug development including market exclusivity, fee reduction, priority application review

For orphan drugs, these common features have allowed the US and EU to collaborate and utilize a [common application process](#) for the designation while continuing to maintain separate approval processes.

Operating in an internationally aligned manner has allowed foreign regulators to maximize limited resources and coordinate their regulatory efforts in other areas including better information sharing in pre-market assessment and monitoring of post-market obligations (e.g. pharmacovigilance).

The design of the Canadian orphan drug regulations would allow Health Canada to operationally align and participate in well-established activities of the US and the EU including designation, scientific/protocol advice and pre- and post-market information sharing. Pooling of resources will be essential for operational efficiency and excellence in science. The lack of internationally aligned activities for orphan drugs has been identified as a burden for orphan drug development in Canada by the [Red Tape Reduction Commission](#) in one of the 90 specific recommendations in its report.

Canadian Context

In the absence of an orphan drug regulatory framework Canadians have been able to access some orphan drugs through Health Canada's Special Access Programme, clinical trials or as new drugs that have received their Notice of Compliance under Part C, Division 8 of the *Food and Drug Regulations*.

While these paths worked in the past they are limited in both providing access to orphan drugs and information gathering and sharing since they were not designed to address the unique challenges of rare diseases.

Proposed Regulatory Framework for Orphan Drugs under the *Food and Drugs Act*

Objective

The objective of the proposal is to establish a comprehensive framework that will provide access to orphan drugs for Canadians without compromising patient safety. This proposal will address the unique challenges of studying small patient populations and align Canadian regulatory activities with those of the international partners.

Overview

The proposal would provide an internationally aligned scheme in regulation that would transparently identify what is an orphan drug and manage the benefits, harms and uncertainties by considering the nature, intended use and exposure of orphan drugs throughout the life-cycle. The life-cycle approach would provide appropriate regulatory oversight from the designation and clinical trial design through to authorization to post-approval monitoring. It would allow for greater opportunity to receive both expert advice and the patient perspective on the severity of the disease to provide greater context in which regulatory decisions are made. This will be accomplished by introducing a broader spectrum of tools to gather and address new information including the ability to intervene through a label change, reassessment, stop-sale, suspension and cancellation of an authorization. This integrated approach will move away from the current static, moment-in-time means of regulating that is found in Part C, Division 8, of the *Food and Drug Regulations* into a more balanced, dynamic and fluid set of interventions that will better serve the patient's needs while maintaining strong safety oversight. This is important for small vulnerable populations that may have no other options available to alleviate their suffering.

As an early deliverable in the [Regulatory Roadmap for Health Products and Food](#), the life-cycle concepts first introduced in this regulatory framework will drive all other modernization efforts for drugs and medical devices that will follow.

The regulation of orphan drugs will rely on many existing provisions of the *Food and Drug Regulations* including for:

- Labelling and packaging (Part A and Part C, Divisions 1, 3 and 4)
- Clinical Trials (Part C, Division 5, with potential exceptions)
- Establishment Licensing and Good Manufacturing Practices (Part C, Divisions 1A and 2, with potential exceptions)
- Market exclusivity (Part C, Division 8)

Recognizing that greater uncertainties may exist for orphan drugs given the complexities of the diseases, the small and vulnerable populations and the treatment environment itself, greater abilities to plan for and resolve those uncertainties are needed once the drug is on the market that will not compromise pre-market authorization requirements.

Greater transparency to improve gathering and sharing of information amongst patients, health care professionals, researchers, payers and international regulatory partners including advancing the quality of knowledge for better decision-making are key components of the new framework necessary to resolve uncertainties.

Key new features of the framework found in other orphan drug regulations include:

Orphan Drug Designation

Designation is a new step intended to be undertaken by Health Canada in the regulatory life cycle of a drug. It is unique to this proposed framework and an equivalent activity is not currently found within the *Food and Drug Regulations*. Designation is a key component of international orphan drug frameworks that enables the holder of a designation to a unique package of regulatory considerations. Health Canada is proposing that this will include scientific and clinical protocol advice, priority review, fee reductions for small to medium enterprises and linkage to the existing market exclusivity of 8 years and six months for innovative drugs that includes the results of pediatric studies. Certain criteria will have to be met including information for prevalence and severity of the disease as well as the lack of existing therapy or significant improvement compared to the current drug treatment. Provisions would also allow a sponsor to submit an application on the basis of designation of a recognized country. Similar to other jurisdictions more than one sponsor may receive orphan drug designation for the same drug for the same rare disease, however each sponsor seeking orphan drug designation must file a complete application. The same drug may also have multiple orphan drug designations for different rare diseases. These measures are intended to facilitate research and innovation in the area of rare disease without restricting activities to a single sponsor or a single drug, thus increasing the possibility of success. Historically, success for an orphan drug reaching the market place has been limited. In the US from 1983 to 2012 only 408 orphan drugs were approved from 2661 designations that were granted during the same time.

Regulatory Advice from Health Canada

Provision that allow the sponsor to submit an application for scientific and clinical protocol advice by Health Canada or in-common with international regulators will be included in this framework. The opportunity to provide this type of formal and structured advice at an early stage in drug development is intended to facilitate the conduct of studies and the collection of information about the drug's benefits, harms and uncertainties thereby increasing the possibility of success at the application stage. In developing this advice Health Canada may seek the opinions of experts and patient representative when such knowledge is not available within the Department. This formal advice can only be changed through an amendment process in a situation such as when new information becomes available that renders the previous advice invalid.

Expert Advice and Patient Representation to Health Canada

As there have been over 7000 rare diseases identified, it follows that regulatory agencies, including Health Canada, cannot maintain the specialized scientific and medical expertise that may be necessary to assess information in support of an application with respect to an orphan drug. Therefore in order to come to the best possible decisions in the interests of Canadian patients, Health Canada may seek expert advice at various points in the regulatory process. It is anticipated that expert advice could be sought from clinicians, academics and foreign regulators

including specialized bodies such as the Committee for Orphan Medicinal Products (COMP) at the European Medicines Agency (EMA). There are currently no provisions under the *Food and Drug Regulations* that give structure to the use of expert advice by Health Canada in decision making processes other than the New Drug Committee under C.08.009. The patient's perspective on the severity of the disease or the unmet medical need in a therapeutic area, including early input into protocol advice, will also bring valuable insight needed to support Health Canada's regulatory responsibilities. Recent updates through the US FDA's *Food and Drug Administration Safety and Innovation Act* improve the ability to seek expert advice and patient's perspective for orphan drugs when targeted consultation is necessary because such knowledge whether scientific, medical or technical in nature is not available internally.

Application for Market Authorization

Application requirements for orphan drugs will be similar to what currently exists in *Food and Drug Regulations*. Significant new requirement that enables transparency would include the prerequisite to provide documentation that all clinical trials were registered on a publically accessible registry, in accordance with international standards. The provision of a post-market plan to support the ongoing assessment of the benefits, harms and uncertainties associated with the drug will strengthen life-cycle management (see Post-Market Plan below). Priority review, similar to Health Canada's current policy, will be granted for orphan drug market authorization applications.

Market Authorization for Orphan Drugs

A Market Authorization is an approval to sell an orphan drug. In contrast to issuing individual Notices of Compliance, a single Market Authorization would be issued for each orphan drug and could be amended, reassessed, suspended or cancelled. Provisions in regulation would be designed to support the transparency to the public of an orphan drug Market Authorization and would include open and accessible publication of the key information including whether an application has been evaluated and a negative decision rendered. The publication of negative decisions and the basis for these decisions is important for orphan drugs in circumstances when an existing marketed re-purposed drug could continue to be used 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, there will be a requirement for a plan to support ongoing assessment and management of the benefits, harms and uncertainties associated with the drug and its use. This builds upon current practices at Health Canada and worldwide whereby manufacturers have been providing the regulator with post-market plans including Risk Management Plans and Pharmacovigilance Plans for review at the time of submission. Similar post-market planning requirements have recently been introduced into regulation for Extraordinary Use New Drugs (EUND, see C.08.002.01(2)(b)(ix)). Having these plans as a regulatory requirement allows for better monitoring and reassessment once the drugs are

marketed. Flexibility in how and in what format the application information is provided to Health Canada needs to allow for different formats such as that which currently exist in the US and EU. This will also enable joint evaluation activities with international partners bringing efficiencies to the process as well as concentrating expertise.

Ability for Minister to obtain information and reassess a market authorization

Health Canada may receive information regarding the benefits, harms and uncertainties of a marketed drug from a variety of sources including directly from the manufacturer. When this new information raises uncertainties or does not resolve existing uncertainties, Health Canada should have the ability to direct the Market Authorization holder to address these through various means including a reassessment of the benefits, harms and uncertainties which may require new studies. The final outcome of the reassessment process could result in no change, an amendment to, or suspension of the Marketing Authorization. The results of the reassessment would be made publically available as this information is an important part of resolving existing or new uncertainties.

Technical Description of the Proposed Regulatory Framework

A. General

Overview and application

A new Division under Part C of the *Food and Drug Regulations* would be created to introduce a regulatory framework for orphan drugs.

The regulatory framework would apply to orphan drugs for human use and include provisions relating to:

- Orphan drug designation
- Regulatory advice
- Expert and patient advice
- Market Authorization
- Post-market authorization obligations and abilities

It would rely, as necessary, on existing drug provisions of the *Food and Drug Regulations*, including those related to:

- Labelling and packaging (Part A and Part C, Divisions 1, 3 and 4)
- Clinical Trials (Part C, Division 5, with potential exceptions)
- Establishment Licensing and Good Manufacturing Practices (Part C, Divisions 1A and 2, with potential exceptions)

- Market exclusivity (Part C, Division 8)

Definitions

Definitions would include a definition of the term “orphan drug” to mean a drug that meets the following criteria:

- a. The drug is intended for the diagnosis, treatment, mitigation or prevention of a life-threatening, seriously debilitating, or serious and chronic disease or condition affecting not more than five in 10 thousand persons in Canada; and
- b. The drug is not currently authorized by the Minister or if currently authorized, it will provide a potentially substantial benefit for the patient distinguishable from the existing therapy.

B. Orphan Drug Designation

Application for orphan drug designation

A sponsor may submit an application for orphan drug designation. The application must be signed and dated by the sponsor and contain the following information:

- a. The name, address and telephone number and, if applicable, the facsimile number and electronic mail address of the sponsor and the sponsor’s representative in Canada in the case of a foreign sponsor;
- b. When available, information on the manufacturer(s) of the drug if the drug is not manufactured by the sponsor;
- c. The medicinal ingredients of the drug;
- d. The proposed indication;
- e. Sufficient information to demonstrate that the criteria under the orphan drug definition are met;
- f. A description of the stage of drug development, including indications expected; and,

- g. A summary of the regulatory status of the drug in Canada and in foreign countries, including current investigational uses, previous market authorizations, orphan drug designation status, and any regulatory actions taken, where available.

Application for orphan drug designation based on a foreign designation

Alternately, a sponsor may submit an application for orphan drug designation on the basis of a designation from a recognized country, if the proposed orphan drug and indication in Canada is the same to that under which the foreign designation was issued. The application must be signed and dated by the sponsor and contain the following information:

- a. The name, address and telephone number and, if applicable, the facsimile number and electronic mail address of the sponsor and the sponsor's representative in Canada in the case of a foreign sponsor;
- b. The medicinal ingredients of the drug;
- c. A copy of the foreign designation;
- d. A statement that:
 - i. The proposed orphan drug and indication in Canada is the same to that under which the foreign designation was issued; and

The criteria under the orphan drug definition are met.

Request for Additional Information

The Minister would be able to request that additional information be provided by a sponsor, within a time specified by the Minister, if the application lacks information or contains inaccurate or incomplete information.

The Minister would be able to consider the application to be withdrawn if the sponsor fails to provide a response by the time indicated in the request, unless the sponsor has requested for an extension and the Minister has agreed to it.

Issuance of an orphan drug designation

The Minister would be required to issue an orphan drug designation in respect of a drug if satisfied that the criteria under the orphan drug definition are met.

Transparency

The Minister would be required to maintain and make available to the public a list of orphan drug designations.

Sponsor's Obligations

The sponsor of an orphan drug designation that was issued on the basis of a designation from a recognized country would be required to report to the Minister any change in the status of the foreign designation that was provided in the application for designation.

Sponsors would be required to notify the Minister when a designation is being transferred to another sponsor and provide updated contact information.

Cancellation of a designation

The Minister would be able to, by notice, cancel a designation when a drug no longer meets the criteria for orphan drug designation.

The sponsor would have an opportunity to make representations prior to the cancellation.

C. Regulatory Advice

A person may submit, at any time in the drug development process, an application for written regulatory advice, which can only be changed through an amendment process, for the purpose of reaching agreement on the type and amount of information required to demonstrate the benefits and harms associated with the use of an orphan.

The Minister would be able to amend the regulatory advice when:

- a. Both the Minister and the person that received the regulatory advice deem it necessary to do so; 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

The Minister would be required to give a sponsor, market authorization applicant or holder an opportunity to make representations when the Minister has sought advice from experts or patient representatives, when necessary, before:

- a. Making a decision to issue, refuse or cancel an orphan drug designation;
- b. Providing regulatory advice in respect of an orphan drug;
- c. Making a decision to issue, amend, refuse to issue or amend, suspend or cancel a market authorization for an orphan drug; or
- d. Making a decision to maintain, amend or suspend a market authorization of an orphan drug that is the subject of a reassessment

NOTE: Experts may include, for example, healthcare providers, scientific and medical experts, buyers, payers, and health technology assessors.

E. Clinical Trials

Orphan drugs to be used for the purposes of clinical trials would be subject to Part C, Division 5 of the *Food and Drug Regulations*, with potential minor modifications.

F. Market Authorization for an Orphan Drug

Application for a Market Authorization

An orphan drug that has been issued a market authorization under this regulatory framework would be exempt from section C.01.014 and subsection C.08.002(1) of the *Food and Drug Regulations*.

A person may submit an application for a market authorization of an orphan drug. The application must contain the 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.
- e. 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 and 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.

An applicant may cross-reference information referred to above if:

- a. The application relates to a new indication for a drug for which a NOC has been issued under section C.08.004 of the *Food and Drug Regulations*, and
- b. The information is not different from that which was originally submitted under C.08.002(2) of the *Food and Drug Regulations*.

Assessment of an application for Market Authorization

The Minister would be required to prioritize the assessment of an application for market authorization for an orphan drug, if the Minister is satisfied that the application has been made in accordance with the application requirements.

The Minister would be able to request that the applicant provides additional information as necessary if the information and documents submitted in the application for market authorization are insufficient to enable the Minister to determine whether the market authorization should be issued.

The Minister would be required to, following the assessment of the application, notify the applicant in writing of any deficiencies if the application does not comply with the requirements and provide an opportunity for the applicant to address the deficiencies by filing additional information.

Market Authorization Issuance

Following the assessment of the application, the Minister would either:

- a. Issue a market authorization if the Minister is of the opinion, taking into account the extent and nature of the uncertainties associated with the benefits and harms and the small size of the patient population, that the benefits associated with the use of the orphan drug outweigh the harms, and that uncertainties of the benefits and harms do not prevent the Minister from issuing the market authorization; or
- b. Refuse to issue a market authorization if:
 - i. The Minister is of the opinion that the harms associated with the use of the orphan drug outweigh the benefits
 - ii. The uncertainties of the benefits and harms prevent the Minister from issuing the market authorization; or
 - iii. The applicant has failed to address the deficiencies in the deficiency notice.

The Minister would be required to notify the applicant of the result of the assessment and decision to either issue or refuse to issue a market authorization.

The applicant would have an opportunity to make representations where the Minister has refused to issue a market authorization.

The Minister would be required to reconsider the decision after giving the applicant that opportunity.

Drug Identification Number

The Minister would be required to assign a drug identification number, preceded by the letters “DIN”, to each orphan drug in respect of which a market authorization is issued.

Contents of Market Authorization

The contents of a market authorization issued by the Minister would be set as follows:

- Name and address of the market authorization holder
- Common name and brand name of the orphan drug
- Recommended conditions of use for the orphan drug
- Drug Identification Number assigned by the Minister
- Label
- Plan summary

Transparency

The Minister would be required to maintain and make available to the public the contents of the market authorization and related annexes (e.g. summary basis of decisions, reassessment results, information related to discontinuances).

The Minister would be required to make available to the public negative decisions.

G. Changes to a Market Authorization

Changes to a market authorization requiring the filing of an amendment application

The sale of an orphan drug that is the subject of a change that requires the filing of an amendment application by a market authorization holder would be prohibited.

The market authorization holder would be required to submit an amendment application including the information set out in the market authorization application section that is relevant to the change, when proposing to make one or more of the following changes:

- a. Any change to the information supporting an orphan drug where that change has the potential to significantly change the benefits, harms and uncertainties associated with the use of the orphan drug;
- b. Any change to the plan authorized under the market authorization;
- c. Changes in any administrative details on the market authorization such as the name or address of the market authorization holder;
- d. Changes to the brand name of the orphan drug.

Assessment of an application to amend a market authorization

The Minister would be able to request that the applicant provides additional information as necessary if the information and documents submitted in the application for market authorization amendment are insufficient to enable the Minister to determine whether the market authorization should be amended.

The Minister would be required to, following the assessment of the amendment application, notify the applicant in writing of any deficiencies if the application does not comply with the requirements and provide an opportunity for the applicant to address the deficiencies by filing additional information.

Amendment of a market authorization

The Minister would be able to, following the assessment of the amendment application to either:

- a. Amend a market authorization if the Minister is of the opinion, taking into account the extent and nature of the uncertainties associated with the benefits and harms and the small size of the patient population, that the benefits associated with the use of the orphan drug outweigh the harms, and that uncertainties of the benefits and harms do not prevent the Minister from amending the market authorization; or
- b. Refuse to amend a market authorization if:
 - i. The Minister is of the opinion that the harms associated with the use of the orphan drug outweigh the benefits;
 - ii. The uncertainties of the benefits and harms prevent the Minister from amending the market authorization; or

- iii. The applicant has failed to address the deficiencies in the deficiency notice.

The market authorization holder would have an opportunity to make representations where the Minister has refused to amend a market authorization.

The Minister would be required to reconsider the decision after giving the market authorization holder that opportunity.

Changes to a market authorization requiring the filing of a notification

The market authorization holder would be required to notify the Minister XX days prior to implementation of any other change to the information supporting the orphan drug that does not affect the benefits, harms and uncertainties associated with the use of the orphan drug.

The market authorization holder would be permitted to implement notified changes XX days following notification unless otherwise directed by the Minister.

NOTE: Need to confirm the number of days for notification and implementation of change

H. Market Authorization Holder's Obligations

The conditions of a market authorization for an orphan drug that would apply to all market authorizations under this new division would be set out as follows and would require a market authorization holder to:

Labelling and packaging

- a. Label and package the orphan drug in accordance with the requirements set out in the *Food and Drug Regulations*;
- b. Show the drug identification number (DIN) assigned by the Minister on the principal display panel of both the inner and outer label of the orphan drug (equivalent requirement to that under section C.01.005 of the *Food and Drug Regulations*);

Good manufacturing practices

- c. Ensure that the orphan drug is manufactured, handled and stored in accordance with the applicable good manufacturing practices referred to in Divisions 2 to 4 of the *Food and Drug Regulations*;

Serious adverse drug reaction reporting

- d. Report to the Minister serious adverse drug reactions within 15 days after receiving or becoming aware of the information (this requirement should be equivalent to that under section C.01.017)

Reporting of new information

- e. Report to the Minister new information which might impact the assessment of the benefits, harms and uncertainties of the orphan drug concerned;

Implementation and maintenance of the plan authorized under a market authorization

- f. Implement the plan authorized under the market authorization, including reporting to the Minister within a time specified in the plan;
- g. Update the plan as necessary when new information becomes available and report of any change by filing an amendment application to the Minister in accordance with the requirements of the new orphan drug regulations;

Recall Reporting

- h. Notify the Minister in accordance with C.01.051 of any recalls of an orphan drug;

Marketing status

- i. Notify the Minister within 30 days after commencing sale of an orphan drug, indicating the date on which the orphan drug was first sold in Canada (similar to the requirement under paragraph C.01.014.3(c));
- j. Notify the Minister of the discontinuation of sale of an orphan drug at least 6 months in advance of a planned discontinuance. The notification should include the company name and contact, product details; and anticipated date of discontinuation.

Annual Notification

- k. Notify the Minister annually in accordance with section C.01.014.5 to confirm that the information previously submitted in the market authorization with respect to the orphan drug is correct;

Changes in regulatory status in other countries

- l. Notify the Minister, within a reasonable delay, of any change in regulatory status in other countries in the following situations:
 - Recall of the drug with the same medicinal ingredient
 - Withdrawal of the drug or an indication
 - Suspension of authorizations

Maintenance of records

m. Establish and maintain records in a manner that enables an audit to be made.

NOTE: Need to identify the types of records required to be established and maintained.

I. Post-market Authorization Abilities

Ability for Minister to request information

The Minister would be able to request a market authorization holder to provide new information concerning an orphan drug that is in his or her possession, if the Minister is of the opinion that this information is necessary to assess the benefits, harms and uncertainties associated with the use of the orphan drug.

Ability for Minister to require a market authorization holder to compile information

The Minister would be able to require, by notice, a market authorization holder to compile information concerning an orphan drug, within a time specified by the Minister, if the Minister is of the opinion that the plan authorized under the market authorization is no longer sufficient to gather the information that is necessary to assess the benefits, harms and uncertainties associated with the use of the orphan drug.

The Minister would be required to give the market authorization holder an opportunity to make representations. After considering any representations, the plan authorized under the market authorization may be amended, if necessary.

Ability for the Minister to require a change to the label or package of an orphan drug

The Minister would be able to require, by notice, a market authorization holder to make a change to the label or package of an orphan drug, within a time specified by the Minister, if the Minister is of the opinion that it is necessary to prevent injury to health or prevent misleading representation.

The Minister would be required to give the market authorization holder an opportunity to make representations.

Ability for Minister to conduct the reassessment of an orphan drug

The Minister would be able to require, by notice, a market authorization holder to provide information to support the reassessment of an orphan drug, within a time specified by the Minister, if information that become available to the Minister indicates a significant and unfavourable change to the benefits, harms and uncertainties of the orphan drug.

The Minister would be required to, after assessing the information provided by the market authorization holder, confirm in writing whether to:

- a. Maintain the market authorization;
- b. Amend the market authorization; or
- c. Suspend the market authorization.

Ability for the Minister to direct a person to stop the sale of an orphan drug

The Minister would have the ability to direct a person or a class or persons to stop the sale of an orphan drug if the Minister is of the opinion that the harms associated with the use of the orphan drug outweigh the benefits.

The Minister would be required to lift a direction to stop the sale of an orphan drug if the circumstances that gave rise to the direction have been addressed.

Ability for the Minister to suspend a market authorization - contravention or harm

The Minister would be able to, by notice, suspend a market authorization for an orphan drug, in whole or in part, if the Minister is of the opinion that:

- a. The market authorization holder has contravened a provision of the Act or the regulations; or
- b. The harms associated with the use of the orphan drug outweigh the benefits.

The Minister would be required to give the market authorization holder an opportunity to make representations prior to the suspension.

The Minister would be required to, after considering any representations, confirm in writing whether to:

- a. Maintain the market authorization;
- b. Amend the market authorization; or
- c. Suspend the market authorization.

Ability for the Minister to suspend a market authorization - immediate suspension

The Minister would be able to, by notice, suspend a market authorization in whole or in part if the Minister is of the opinion that an immediate suspension is necessary to respond to a serious and imminent risk of injury to health.

The market authorization holder would have an opportunity to make representations any time following the suspension.

The Minister would be able to do the following, after considering any representations, if he or she is of the opinion that the market authorization holder has addressed the initial grounds for suspension, as identified in the suspension notification:

- a. Reinstate the market authorization; or
- b. Reinstate and amend the market authorization.

Ability for the Minister to cancel a market authorization - contravention

The Minister would be able to, by notice, cancel a market authorization, in whole or in part, if the Minister is of the opinion that the market authorization holder has contravened a provision of the Act or the regulations in respect of an orphan drug and cannot remedy the contravention.

The market authorization holder would have an opportunity to make representations, prior to the cancellation.

The Minister would be required to, after considering any representations, confirm in writing whether to:

- a. Maintain the market authorization;
- b. Amend the market authorization; or
- c. Cancel the market authorization.

Ability for the Minister to cancel a market authorization – benefits do not outweigh harms

The Minister would be able to, after requesting a market authorization holder to establish, within a time specified by the Minister, that the benefits associated with the use of the orphan drug outweigh the harms, cancel, by notice, a market authorization, in whole or in part, if the Minister is of the opinion that the holder has failed to do so.

Ability for the Minister to cancel a market authorization – consent

The Minister would be able to cancel a market authorization, in whole or in part, at the request of its holder.

J. Market exclusivity

The existing data protection provisions under section C.08.004.1 of the *Food and Drug Regulations* and requirements of the *Patented Medicines (Notice of Compliance) Regulations* would apply to a market authorization issued for an orphan drug, including certain amendments to one.