

AN ORPHAN DRUG FRAMEWORK (ODF) FOR CANADA

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INTRODUCTION

A rare disease is a life-threatening, seriously debilitating, or serious and chronic condition that affects a relatively small number of patients (no more than 1 in 2,000).¹ There have been 6,000 to 7,000 rare diseases identified worldwide.¹ An estimated 80% of rare diseases are genetically-based, while the remainder are a result of viral or bacterial infection or other environment causes. More than half of rare diseases start in early childhood² and are degenerative and life-threatening in nature. Although the number of patients affected by each rare disease is small, total number of patients affected by the thousands of rare diseases identified is large. In Canada, one in every 12 Canadians is affected by a rare disease.³

An orphan drug is a pharmaceutical or a biological drug that is used to treat a rare disease. Taking the numbers on orphan drugs into consideration, the following scenario is likely an everyday occurrence in cities across Canada - a parent takes his or her child to their doctor's office with questions about a health concern, and within a few weeks or months, after repeated visits with medical specialists, the family receives the news that their child has a rare genetic disorder. Maybe the diagnosis is retinitis pigmentosa, a condition that causes night blindness in the early stages and gradual loss of peripheral vision, affecting one in every 4,000 people; or perhaps it is Duchenne muscular dystrophy, a neuromuscular disease that affects one in every 3,300 boys and causes rapidly progressive muscle weakness and wasting due to degeneration of skeletal, smooth and cardiac muscle.⁴ Diagnoses of this type are devastating for

the affected families and bring into focus the frequent absence of validated therapies.

Meanwhile, in a research laboratory of a children's hospital in Ontario, there are researchers whose work may lead to effective treatment for these rare genetic diseases, providing hope to families of these rare disease patients. The Children's Hospital of Eastern Ontario's NeuroRARE Disease Research Group is a group of researchers dedicated to identifying the genetic mutations that may cause diseases such as certain forms of epilepsy, neuropathies, ataxias and muscle disorders.⁵ Recently announced funding from the Canadian Institutes for Health Research⁶, along with the Minister of Health's announcement of the development of a Canadian orphan drug framework⁷, is intended to help translate these scientific discoveries into meaningful results for Canadian rare disease patients.

BACKGROUND

Historical and international perspective

Most developed countries have orphan drug policies to deal with the challenges of developing drugs for and studying drugs in small patient populations. Notably, the United States and the European Union have well established orphan drug frameworks that include a process for the designation of an orphan drug, provision of protocol development advice by the regulator, financial incentives, such as research grants in the US⁸⁻⁹ and, in Europe, market exclusivity and fee reductions.¹⁰⁻¹²

Since the US government passed the Orphan Drug Act in 1983, more than 350 orphan

drugs have been developed and brought to the US market.¹³ In the last two decades, a steady average of fourteen new orphan drugs per year has been approved by the US Food and Drug Administration (FDA).¹⁴

The European orphan drug program has been in place since 2000 and has successfully helped bring to that market many of the same drugs that have been approved in the US. In its first decade, the Committee for Orphan Medicinal Products of the European Medicines Agency (EMA) designated 850 drugs as promising treatments for rare diseases and granted market authorizations to more than 60 orphan drugs.¹⁵

Canada

Canada is one of only a few developed countries without a regulatory framework for orphan drugs. In the absence of a specific framework, Canadians were able to access many orphan drugs through Health Canada's Special Access Programme, through clinical trials or as drugs approved through the regular new drug submission process (often under the Notice of Compliance with Conditions policy). While this patchwork approach has worked sufficiently in the past, there are limitations both in providing access to orphan drugs and in gathering data and sharing information about the use of these drugs in the post-market period. Currently, none of the existing Canadian regulations are specifically designed to address the challenges presented by rare diseases, sometimes leaving Canadian patients without access to medications that could help them.

The FDA approved 99 different drugs with orphan indications between January 2008 and May 2013.¹⁶ Based on data gathered from Health Canada's databases, as of May 2013, market authorizations have been issued for 51 of the 99 orphan drugs approved by the US.¹⁷ Health Canada's Special Access Programme issued authorizations for 21 of the remaining 48 non-marketed drugs between Jan 2012 and June 2013.¹⁸

On October 3, 2012, the Minister of Health announced two initiatives to help Canadians with rare diseases: the creation of a new regulatory framework for orphan drugs and

the launch of the Canadian portal to Orphanet, a comprehensive online database of information about and services for rare diseases. Since the Minister's announcement, Health Canada has engaged a group of scientists, medical and clinical trial experts and policy makers from within the Department to develop regulations, guidance documents and operational plans around a new orphan drug framework (ODF). In March 2013, a two-day workshop entitled *Developing a Scientific Vision to Support the New Orphan Drug Framework in Canada* was cohosted by Health Canada and the Canadian Institutes for Health Research. In May 2013, a similar workshop, *Oncology and Rare Disease Framework*, was held to discuss scientific challenges and opportunities in the field of rare cancers. The input from scientific experts at these two meetings will help inform many policy decisions by Health Canada.

The framework will also take into account cross-cutting issues raised in the *2011 Fall Report of the Auditor General of Canada*¹⁹ and the first two of four Senate reports about Health Canada's role in the regulation of drugs – *Canada's Clinical Trial Infrastructure: A Prescription for Improved Access to New Medicines*²⁰ and *Prescription Pharmaceuticals in Canada: Post-Approval Monitoring of Safety and Effectiveness*.²¹ All three of these government reports addressed the need for Health Canada to do more to protect the safety of patients, both at the clinical trial stage and in the post-approval period. The first Senate report made a number of recommendations around the transparency of information about Canadian trials but also included a recommendation that regulations be made to support the approval of drugs for rare diseases in Canada. The policy development for Canada's ODF will address all the pertinent recommendations from these reports.

Overview of proposed Canadian framework

Health Canada is working towards a new regulatory framework for orphan drugs that would span the lifecycle of the drug. The regulations would set the criteria for orphan drug designation - to be aligned to the greatest extent possible with those used by the EMA and FDA- and outline the requirements for market authorization and mandate post-market oversight of the use of the

orphan drug. Health Canada will allow for flexibility in the design of trials and in the evaluation of those results in order to accommodate smaller patient populations. In order to gather further information about the benefits, harms and uncertainties of the drug as it is used in a wider population, Health Canada will place a greater emphasis on post-market activities for orphan drugs.

The key objectives of this framework are to provide Canadians with better, timelier access to orphan drugs and to encourage and facilitate clinical research in the area of rare diseases. Facilitation of transparent flow of information between stakeholders (industry, researchers and other government agencies) and Health Canada will help achieve these objectives. The needs of patients with rare diseases will be taken into consideration by Health Canada by allowing patient input throughout the product lifecycle: at the designation, market authorization application review and reassessment stages. Registration of clinical trials, along with opportunities for patients to provide feedback on the safety and effectiveness of the drug, will be important patient-centred components of the ODF.

Designation

This is a regulatory step that would be introduced for the first time in the *Food and Drug Regulations* in the ODF. The regulations would set out the criteria that a rare disease and an orphan drug must meet, and Health Canada would then be able to review an application for designation and render a decision to designate the candidate drug as an orphan drug. The US and Europe both have designation steps built into their regulations.

Clinical trials

The clinical testing of orphan drugs would be governed by the current clinical trials framework (Part C, Division 5 of the *Food and Drug Regulations*). There will also be a requirement for the registration on an acceptable registry (e.g. clinicaltrials.gov) of any clinical trial intended to support a Canadian orphan drug market authorization application.

Scientific advice

The holder of an orphan drug designation would be able to request scientific advice from the regulator on topics such as the acceptability of proposed clinical trials and how to overcome challenges associated with designing studies for small patient populations. Scientific advice may also be sought on other topics not related to clinical trials, including dosage form development, quality issues, preclinical studies and post-market study design.

Submission of an application for market authorization

The type of information and format would be similar to that required for New Drug Submissions for other drugs.

Post-market plan

The market authorization application would have to include a post-market plan that the manufacturer of the orphan drug would have to follow. This plan would include a risk-management plan and could also include ongoing patient monitoring, ranging from establishment of patient registries to the conduct of confirmatory studies in the post-market period. Each plan would be tailored to the benefit-harm-uncertainty profile of the orphan drug at hand. A flexible design will help ensure that high-quality data is generated and reported, so as to minimize the burden on the system while providing adequate post-market oversight for these drugs.

International collaboration

One of the main goals of the Canadian framework will be to align as closely as possible to existing frameworks that are already in place in other jurisdictions, thereby allowing for collaboration with international partners. The EMA and the FDA started working together in 2008 by allowing applications for orphan drug designations to be submitted in parallel and, in some cases, providing parallel protocol advice to orphan drug researchers. In 2012, the EMA and the Japanese

regulatory authorities began working together on orphan drug designation, and this led to an observed increase in the number of Japanese orphan drug designations.²²

Dialogue with officials from other jurisdictions will allow Health Canada to learn from their experience and build an ODF that is well aligned, both scientifically and operationally, with regulators in Europe and the US. This will allow the pooling of information gathered around the world, which will be critical in forming a clearer picture about the benefits, harms and uncertainties associated with the use of an orphan drug, especially for diseases that affect a very small number of patients. Ideally, regulatory cooperation would begin at the designation stage, carry through a product's clinical development phase and continue through the product lifecycle to the post-market stage. Collaboration with the EMA and FDA will likely begin with a common application process for orphan designation and the provision of common trial design advice, so it is vital that the Canadian framework aligns closely with those in place in those other jurisdictions.

A focus on rare disease patients

The proposed framework will allow rare disease patients in Canada to be heard since patient input at the designation stage will be mandated. This is the stage at which Health Canada will be assessing, among other considerations, the unmet medical need for the candidate orphan drug. Also, at the drug review stage, patient input may be sought to confirm that the information gathered at the designation stage is still relevant, and when possible, learn about patients' personal experiences with the candidate drug in clinical trials. Health Canada intends to model its patient input process on those developed by the Canadian Agency for Drugs and Technologies in Health (CADTH).²³ CADTH allows patients to provide their perspective, in a structured and formal manner, on issues such as the severity of the disease and the nature of the unmet medical need.

If there is a need to reassess the safety and effectiveness of an orphan drug in the post-market period, patients will again be provided an opportunity to provide input. Patient feedback would be a critical source of information in any

Health Canada decisions around label changes (e.g. warnings, contraindications) or changes to market authorization status. Collaboration and cooperation with other decision makers in the Canadian healthcare system will be crucial to the success of the proposed ODF.

CONCLUSION

As of the publication date of this article, Health Canada's work on the ODF continues. Cooperation and collaboration with foreign drug regulators and domestic partners in the health system will be important factors. The goal is to bring forward a streamlined, science-based framework that encourages innovation and research, addresses the benefits, harms and uncertainties of the drugs at hand, but also best serves the needs of Canadians living with rare diseases.

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