



The Canadian Rare Disease Therapies Landscape:
Bridging Opportunity to Reality

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INTRODUCTION

In recent years, great strides in research have been achieved in the field of rare diseases in Canada and internationally. In particular, a number of Canadian biopharmaceutical companies and institutional researchers have developed drugs for rare diseases (DRDs) that are saving and improving patients' lives. Many others are at the cutting edge of genetics research and personalized medicine, and are bringing forward the promise of life-saving medicines for Canadians impacted by rare disorders with no current therapies for their condition.

Significant scientific progress has been made in Canada and abroad. Research and development, commercialization and patient access related to DRDs is, however, more challenging than conventional therapies and medicines. As Canada starts to address some of the challenges, stakeholders in the rare disease community are working together to ensure the policy and regulatory environment promotes innovation in the area of rare diseases. This type of environment will enable researchers and biotechnology companies to find better health care solutions for patients suffering from severe conditions so that they can have access to the same high quality of treatment as other Canadians across the country.

Over the last thirty years, many countries have adopted measures to promote the commercial development of DRDs and facilitate patient access to these treatments. Against this background, and given recent developments in the area of rare diseases in Canada, it is timely to assess what has been accomplished so far and to seek to align all the elements required to implement a successful public policy for DRDs in this country.

This paper starts by presenting the context related to orphan diseases and drugs and proposing core principles to help guide the development of DRD initiatives. The paper then explores five elements that need to be included in a comprehensive approach to DRDs, namely: (1) research; (2) regulatory environment and intellectual property; (3) health technology assessment (HTA); (4) reimbursement; and (5) health system adoption.

The purpose of this paper is not to provide complete solutions to all challenges posed by DRDs, but rather to raise opportunities and considerations on how to best move forward in improving the development of, and access to, DRDs in Canada.

EXECUTIVE SUMMARY

- Rare diseases are typically severe conditions affecting a very small proportion of the population.
- Patients with rare diseases face a number of challenges, including the reality that a vast majority of these diseases do not currently have any effective treatment or any treatment in development.
- Approximately half of treatments for rare disorders approved in the United States are currently approved for sale in Canada. In addition, for those that do enter the Canadian market, it can take up to six years to do so following approval in the United States.
- DRDs generally tend to be more costly than more common therapies on a per patient basis given the small market size. Their budget impacts, however, is low because of the rarity of the conditions and the small patient population. As well, based on recent economic analyses, concerns about unsustainable growth in DRD expenditures do not appear to be justified.
- Canada's approach to rare diseases and DRDs should be premised on the following core principles:
 - patient-centeredness
 - expert involvement at all stages
 - national and international collaboration
 - regulatory and economic incentives to encourage innovation
 - comprehensiveness in addressing the following five facets: research, regulatory environment and intellectual property, HTA, reimbursement and health system adoption
- In recent years, Canada has invested heavily in research initiatives and has developed a draft regulatory framework for the designation, authorization and monitoring of DRDs.
- The regulatory framework is a mechanism for successful patient care, while integrating world class research into development by strengthening Canada's approach to DRDs.
- In particular, there are three key areas that would need to be addressed to improve patient access to DRDs and establish a better environment for innovation and investment:
 - **Intellectual Property:** While most jurisdictions with orphan drug frameworks provide a market exclusivity period for DRDs ranging from 7 to 12 years, this incentive is currently not granted to manufacturers in Canada. This is an important gap, as market exclusivity has been highly effective in encouraging the development of DRDs. It is in large part due to this incentive that manufacturers are able to recoup their investments through sales of a new DRD, despite a small market size or patient population.
 - **HTA:** In reviewing DRDs for comparative clinical and cost effectiveness, the Canadian Agency for Drugs and Technologies in Health (CADTH) applies the same standards and processes used in the evaluation of medications for more common diseases. This is a significant challenge, as conventional HTA standards are not suited for assessing DRDs.

A tailored and transparent assessment system that takes into account the unique characteristics of DRDs would be in the best interest of all stakeholders as it would facilitate patient access, foster innovation and help public drug plans make more informed reimbursement decisions.

- **Funding:** Coverage of DRDs is often more restrictive than for standard therapies, and there are significant disparities in coverage across the country. Canada lacks a transparent and consistent funding approach that delivers more equitable and timely access and enhanced benefits to patients with rare diseases.

CONTEXT – DRDs ARE RARER THAN THE ILLNESSES THEY SEEK TO TREAT

The definition of rare diseases varies from one jurisdiction to another. Health Canada defines the term as follows: “*a rare disease is a life-threatening, seriously debilitating, or serious chronic condition that only affects a very small number of patients (typically less than 5 in 10,000 persons).*”¹ This definition is aligned with the definition used in Europe. It is, however, more restrictive than the United States’ definition, which uses roughly the same prevalence but does not require that the disease be “life-threatening, seriously debilitating or a serious chronic condition”. (Table 1 outlines the definition of rare diseases across various jurisdictions.)

According to European statistics rare diseases affect 6-8% of people,² and in Canada one out of 12 people suffer from a rare disease.³ Patients with rare diseases face significant challenges, including delays in diagnosis, the severe impact of the disease on their autonomy and quality of life, difficulties in obtaining appropriate care, the absence of treatment or cure and, in cases where there are available therapies, challenges in accessing them.⁴ For instance, according to the Canadian Organization for Rare Disorders (CORD), only 60% of treatments for rare disorders approved in the United States and Europe are currently available in Canada and most of them get approved up to six years later than in the United States and Europe.⁵ As well, according to Health Canada, as of May 2013, market authorizations had been issued for only 51 of the 99 orphan drugs approved by the United States between January 2008 and May 2013 (i.e., approximately half).⁶

DRDs (also known as orphan drugs) are typically biologic or small-molecule drugs used to treat rare diseases. There are 452 medicines and vaccines in development for rare diseases.⁷ While this is encouraging news for patients with rare diseases, this does not mean that there will be an unsustainable growth in DRD expenditure in the future. The majority of these treatments will not make it through clinical trials and ever be authorized for sale. Second, even for DRDs that do get approved and commercialized, their impact on overall drug budgets will remain relatively low according to recent analyses (more details on these analyses are provided in the section of this paper on reimbursement).

Most developed countries have adopted legislation, policies and strategies to improve access to DRDs. While Canada lags behind other countries in this area, it has started to take positive steps towards facilitating access to DRDs, including supporting research initiatives, developing a regulatory framework (expected to be implemented in 2015), exploring alternative ways to evaluate DRDs at the provincial level and striking an inter-provincial working group to examine

¹ Health Canada’s website: http://www.hc-sc.gc.ca/ahc-asc/media/nr-cp/_2012/2012-147a-eng.php

² Eurordis’ website: <http://www.eurordis.org/content/what-rare-disease>

³ Canadian Organization for Rare Disorders’ (CORD) website: <http://www.raredisorders.ca/aboutUs.html>.

⁴ Eurordis’ website, *supra* note 2.

⁵ CORD’s website: <http://www.raredisorders.ca/currentIssues.html>.

⁶ Lee, D. et al., *An Orphan Drug Framework (ODF) for Canada*, J Popul Ther Clin Pharmacol Vol 21(1): e42-e-46, February 23, 2014:

http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0CB8QFjAA&url=http%3A%2F%2Fwww.jptcp.com%2Fjtpcpe42_e46_wong2-r199353&ei=OASGVPfYH8qSyASzrlHoAg&usq=AFQjCNE4kVm9feNvegbBnDHkZ3BgmU6onw&bvm=bv.80642063,d.aWw

⁷ PhRMA, *2013 Report on Orphan Drugs in the Pipeline*:

http://www.phrma.org/sites/default/files/pdf/Rare_Diseases_2013.pdf

funding approaches. Building on this momentum, governments, industry, patients and healthcare providers can work together to improve access to DRDs based on the following core principles:

Patient-centered

Any approach to DRDs needs to put patients first and provide timely access to the medicines that they need. A key principle driving any approach should be that patients suffering from rare diseases across the country are entitled to the same high quality of healthcare as other patients.

Expert Involvement

Given the limited knowledge available with regard to rare conditions and their treatments, experts with real-life experience need to be involved at all stages, including regulatory approval, HTA, reimbursement and post-market studies related to DRDs. In particular, decision-making processes should seek the input of clinical experts who have experience with patients with rare disorders and DRDs.

Collaboration

While recognizing different levels of review call for different types of evidence, all stakeholders from the rare disease community (including regulators, HTA evaluators, payers, healthcare professionals, researchers, patients and the life sciences industry) need to work collaboratively at the national and international level to exchange knowledge and best practices. This will avoid inconsistencies in assessments and decisions and ensure the best available use of the expertise and data in this area. This is especially important in the field of rare diseases where patient populations are very small and where the natural history of the diseases may not be well known. In order to promote collaboration, processes for approving, reviewing and reimbursing DRDs need to be aligned within Canada and be consistent with those of other countries.

Innovation Incentives

World leading research in rare diseases is being conducted in Canadian hospitals, research institutions and many SME biotechnology companies. An integrated approach offering globally competitive regulatory performance and financial incentives is needed to ensure this research leads to effective therapies. Approaches to HTA and reimbursement also need to be appropriately tailored to DRDs to allow for more predictable market and patient access conditions for biotechnology companies to secure the long term investment required to bring therapies to market.

Comprehensive

While government roles may be different between federal and provincial/territorial levels, public DRD initiatives need to be appropriately linked and coordinated to form a comprehensive approach that addresses the following five key facets: (1) research; (2) regulatory environment and intellectual property; (3) HTA; (4) reimbursement; and (5) health system adoption.

Alexion Pharmaceuticals is developing a breakthrough therapy known as asfotase alfa, a first-in-class targeted enzyme replacement for Hypophosphatasia (HPP), an inherited and life-threatening ultra-rare metabolic disorder that leads to progressive damage to multiple vital organs, including destruction and deformity of bones. Asfotase alfa was initially developed by the Montreal-based Enobia Pharma Inc., which became part of Alexion in 2011. A significant portion of the research and development for this treatment was undertaken in Canada, and Canadian clinicians now have global expertise in the treatment of HPP.

Amorfix Life Sciences Ltd. is an early-stage product development company focused on therapeutic products and diagnostic devices targeting misfolded protein diseases, including Amyotrophic Lateral Sclerosis (ALS), cancer and Alzheimer's Disease.

RESEARCH

In Canada, the biopharmaceutical industry has been involved in conducting important research to develop DRDs.

Governments, research institutes and not-for-profit organizations have also been supporting rare disease research in Canada:

- In 2012, the federal government's Canadian Institutes of Health Research (CIHR) created a national entry to the Orphanet web portal, which provides information on rare diseases and treatments.⁸
- In 2012, CIHR funded nine collaborative research teams, which investigated a range of issues related to rare diseases, including basic biological science, health services, and policies.⁹
- CIHR and Genome Canada, a non-for-profit organization in part funded by the federal and provincial governments, also supported the project FORGE (Finding of Rare Disease Genes in Canada). This consortium made great strides in the area of genetic discovery by

⁸ See <http://www.orpha.net/national/CA-EN/index/homepage/>.

⁹ CIHR press release and related fact sheet, 2012: <http://www.cihr-irsc.gc.ca/e/44944.html> and <http://www.cihr-irsc.gc.ca/e/44945.html>.

identifying disease-causing variants for 146 pediatric disorders over a 2-year period (2011-2013).¹⁰

- Canadian researchers have been seeking funding for their projects with European labs through the E-Rare 2 initiative, which includes CIHR and the Fonds de Recherche Québec – Santé (a not-for-profit funding agency of the government of Québec) as members.
- CIHR and Genome Canada are part of the International Rare Diseases Research Consortium, which brings together funders to support rare disease research.
- The Care for Rare program, includes partners such as CIHR, Genome Canada, the Ontario Genomics Institute (a not-for-profit organization) and also the pharmaceutical industry. This program is a pan-Canadian team of clinicians, bioinformaticians, scientists and researchers focused on improving clinical care for patients and families affected by rare diseases.¹¹
- In 2014, CIHR, in partnership with Genome Canada, awarded the Canadian Rare Diseases Models and Mechanisms Network \$2.3 million to investigate the molecular mechanisms of rare diseases.¹²

BELLUS Health is a drug development company, located in Laval, Quebec, focused on rare diseases. Its lead program KFACTA is currently in a Phase III Confirmatory Study for the treatment of AA amyloidosis, an orphan indication resulting in renal dysfunction that often leads to dialysis and death.

Continued investment in research is critical to improve the scientific understanding related to rare diseases required to achieve optimal patient care. More specifically, investments in this area should include supporting: (1) research on rare diseases, such as genetic, epigenetic and pathophysiological studies; (2) development of applications for diagnosis, such as identification and characterization of (bio)-markers for diagnosis and prognosis, development of innovative screening systems and diagnostic tools/tests; and (3) development of therapies for rare diseases.

Rare disease research is complex and expensive, given the small population and limited available knowledge on the diseases. As discussed below, governments can help provide an enabling environment, including regulatory and financial incentives, to encourage biotechnology companies to invest in research and development of DRDs. In addition, ongoing government investment in research and academic institutions facilitates much needed international collaboration and private-public partnerships in the field of rare diseases. By bringing together committed public funders, academia, medical research not-for-profit organizations and the biopharmaceutical industry, Canada can play a leading role in this area in the future.

¹⁰ Beaulieu C.L. et al., *FORGE Canada Consortium: Outcomes of a 2-year National Rare-Disease Gene-Discovery Project*, Am J Hum Genet., June 5, 2014; 94(6): 809–817: <http://www.ncbi.nlm.nih.gov/pubmed/24906018>.

¹¹ MacLeod S.M. et al., *The Study of Drugs for Rare Disorders: Harnessing Research Contribution by Canadian Academic Institutions*, J Popul Ther Clin Pharmacol Vol 21(1): e47-e55; February 23, 2014: http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0CB8QFjAA&url=http%3A%2F%2Fwww.jptcp.com%2Fjptcp_e47_e55_macleod-pdf-r199354&ei=jgGGVLeMloiGyQSSoLYBg&usg=AFQjCNGpwc6YI65fXRYMT-Yr1bSaqeAdMA&bvm=bv.80642063,d.aWw.

¹² Genome Canada website, press release, November 2014: <http://www.genomecanada.ca/en/about/news.aspx?i=514>.

REGULATORY ENVIRONMENT AND INTELLECTUAL PROPERTY

As Canada moves towards addressing the long-standing gap of care for patients with rare diseases, relying solely on the current Canadian drug approval system and commercial environment will not lead to increased DRD development and access. Under normal market conditions, it is challenging to develop DRDs, as investments in these treatments may not be recovered by projected sales given the small size of the potential market.

This is why many jurisdictions worldwide have established DRD regulatory and intellectual property frameworks. The United States was the first country to enact orphan drug legislation in 1983, followed by Japan (1993), Australia (1997), the European Union (1999) and Taiwan (2000).

These orphan drug regimes have stimulated research and development for DRDs by providing clear regulatory pathways and direct incentives, including fee reductions, regulatory assistance, market exclusivity, accelerated reviews, funds to promote research, tax incentives and scientific advice for the design of clinical programs. To qualify for these incentives, most jurisdictions require applicants to obtain an “orphan designation” for their proposed medication. (**Table 2** outlines key regulatory and economic incentives provided across various jurisdictions.) This designation can serve to stimulate investment interest, align research capacity among institutions and facilitate clinical trial design and access.

These frameworks have been successful, as hundreds of more DRDs have been developed and approved since their adoption. For example, prior to the orphan drug legislation in the United States, only ten DRDs were approved.

Today, there are more than 400. The European Union saw a wave of approvals since European countries collectively adopted orphan drug policies, jumping from eight products to over 70, today.¹³

At the time of writing, Canada still does not have a regulatory framework for DRDs.¹⁴ This, however, is about to change. In 2012, Health Canada announced that it would implement a regulatory pathway for orphan drugs. This framework will focus on the following key elements:¹⁵

DelMar Pharmaceuticals, located in Vancouver, develops and commercializes cancer therapies in new orphan drug indications where patients are failing or have become intolerable to modern targeted or biologic treatments. VAL-083, the company's leading product, is currently undergoing clinical trials as a potential treatment for refractory glioblastoma multiforme (GBM), the most common and aggressive form of brain cancer.

¹³ Franco, P., *Orphan drugs: the regulatory environment*, Drug Discovery Today, Vol. 18, Numbers 3/4, February 2013: <http://www.sciencedirect.com/science/article/pii/S1359644612003030>.

¹⁴ Many Canadians are currently accessing DRDs through Health Canada's Special Access Program, which is not specifically designed to address challenges related to DRDs. This means that many Canadians have not been able to access DRDs. See Lee, D. et al., *supra* note 6.

¹⁵ Health Canada, Office of Legislative and Regulatory Modernization, *Initial Draft Discussion Document for A Canadian Orphan Drug Regulatory Framework*, December 13, 2012: http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact=8&ved=0CB8QFjAA&url=http%3A%2F%2Fwww.orpha.net%2Fnational%2Fdata%2FCA-EN%2Fwww%2Fuploads%2FInitial-Draft-Discussion-Document-for-A-Canadian-Orphan-Drug-Regulatory-Framework.doc&ei=AAWGVpujINSdygTfzoDgBw&usg=AFQjCNG-6l_wJcp_d1PDDKIKmV_yA5l1GQ&bvm=bv.80642063,d.aWw. See also Lee, D.K. et al., *supra* note 6.

Designation

Regulations will set the criteria a rare disease and an orphan drug must meet. According to Health Canada's draft discussion document for the orphan drug regulatory framework, the term "orphan drug" would mean a drug with 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.

The prevalence used in this definition (i.e., 5 in 10,000) is aligned with the prevalence used by the European Union and close to the prevalence used by the United States (drugs for disorders affecting fewer than 200,000 people in the United States). Health Canada is also expected to adopt a mutual recognition procedure with the European Union and the United States, so that designation in one jurisdiction would facilitate or fast track designation in others.

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).

Scientific advice

The holder of an orphan drug designation can request scientific advice from Health Canada to assist in designing and implementing appropriate clinical trials. Further, when necessary, Health Canada is planning to seek advice from external experts to assist in making the best possible regulatory decisions for these drugs.

Genzyme Canada Inc., based in Mississauga, Ontario, makes significant clinical research investments in Canada every year, involving Canadian principal investigators contributing to the development for new therapies in Gaucher, Fabry, MPS 1, Niemann-Pick and Pompe Diseases.

Application for market authorization

Application requirements for DRDs will be similar to what currently exists in the *Food and Drug Regulations*. Health Canada is expecting to offer fee reductions for small to medium enterprises and to grant priority reviews, similar to its current policy, to orphan drug market authorization applications.

Post-market plan

Market authorization applications will need to include a post-market plan that would be tailored to the benefit-harm-uncertainty profile for the DRD in question. This plan would include a risk-management plan and could also include ongoing patient monitoring.

ImStar Therapeutics is a private biotechnology company with operations in Vancouver and Quebec City developing a new approach to treat patients with Amyotrophic Lateral Sclerosis (ALS), or Lou Gehrig's Disease. The company's lead drug candidate, IMS-088, is the first in a series of novel compounds designed to address a key immune system activation pathway involved in neurodegeneration.

Collaboration

One of the key goals of this regulatory framework is to align as closely as possible to regulatory frameworks already established in other jurisdictions to enable collaboration at the international level. This will allow Canada to learn from other jurisdictions' experiences and also enable the pooling of information related to DRDs.

Patient focused

Patient input will be required at the designation stage, where Health Canada will be assessing, among other issues, the unmet medical need. Patient input may also be sought at the drug review stage to confirm that the information obtained at the designation stage is still relevant and to learn about patients' experiences with the proposed drug in clinical trials. Patient input would also be sought if there is a need to reassess the safety and effectiveness of a DRD in the post-market period. The process for patient input will be modeled on the one developed by CADTH. In August 2014, Health Canada launched a pilot project targeting patient input from Canadians with rare diseases to help inform future reviews of orphan drugs.¹⁶

Once implemented, this regulatory framework will be a positive first step in helping facilitate access to DRDs. Canada is seeking to establish a competitive regulatory regime comparable to those found in the European Union and the United States. The orphan drug regulatory frameworks, combined with the economic incentives established in these jurisdictions, have successfully encouraged research in DRDs and brought modern treatment solutions to patients where previously there had been none.

However, in comparison with other jurisdictions worldwide, Canada's proposed approach is missing a crucial feature: market exclusivity. Market exclusivity has been defined as follows: "*The market exclusivity is a period of time during which a medicinal product, that is similar or the same and for the same therapeutic indication as an authorized orphan drug, cannot be validated and authorized by a regulatory competent authority.*"¹⁷ The United States, the European Union, Taiwan and Japan all provide a market exclusivity period for DRDs ranging from 7 to 12 years, depending on the jurisdiction and the type of treatment (see **Table 2** for more details on this). Market exclusivity is the most important incentive for DRD sponsors, as it is in large part due to this incentive that sponsors are able to recoup their investments through sales of a new DRD, despite a small market size or patient population.

¹⁶ Government of Canada, News Release, August 2014: <http://news.gc.ca/web/article-en.do?mthd=index&ctr.page=1&nid=873619>.

¹⁷ Franco, P., *supra* note 13.

Market exclusivity does not mean it is not possible to have more than one treatment for the same orphan indication approved with the market exclusivity. Typically, market exclusivity precludes the entry on the market of the same or “similar” DRD for the same indication. In other words, a non-similar DRD could seek to obtain a market authorization for the same indication as a previously approved DRD.¹⁸ Further, an exception to market exclusivity is typically provided to allow a similar drug to a previously approved DRD to enter the market and enjoy a period of market exclusivity if the drug is deemed to be clinically superior.

Building on its proposed initial regulatory framework, the federal government should consider providing a market exclusivity period for DRDs, beyond the existing data protection. This would help foster and facilitate clinical research in the area of rare diseases, optimize patient access to DRDs and more closely align the Canadian DRD regime to that of the European Union and United States. The federal government has expressly recognized the importance of harmonization with other countries in the context of DRDs.¹⁹

In addition to market exclusivity, the federal government should consider providing other important financial incentives to enhance its regulatory framework, such as tax incentives and additional funds to promote research on orphan drugs. For instance, in United States, there is a 50% federal tax credit for clinical research. In addition, the FDA has a grant program that supports the clinical development of orphan drugs. Also in the United States, the National Institute of Health supports some research in the field of orphan drugs.²⁰

Medunik Canada is a Canadian pharmaceutical company that makes orphan drugs available to Canadians by partnering with international companies to bring products to Canadian patients in need of otherwise unavailable treatments. Medunik Canada's main therapeutic areas include hyperammonaemia due to N-acetylglutamate Synthase (NAGS) deficiency and other urea cycle disorders (UCD).

HEALTH TECHNOLOGY ASSESSMENT

HTA has become an important component of the reimbursement review and approval process. In Canada, HTA is performed by a number of organizations, including CADTH, Quebec’s Institut national d’excellence en santé et en services sociaux (INESSS), provincial committees, hospital committees and various bodies supporting private payers. Private and public payers rely on the reimbursement recommendations made by these HTA bodies to decide what medicines to pay for.

¹⁸ Hughes-Wilson W. et al., *Paying for the Orphan Drug System: break of bend? Is it time for a new evaluation system for payers in Europe to take account of new rare disease treatments?*, Orphanet Journal of Rare Diseases, 7:74, 2012: <http://www.ncbi.nlm.nih.gov/pubmed/23013790>.

¹⁹ Health Canada, *supra* note 15.

²⁰ Franco, P., *supra* note 13.

Payers understandably want an evidence-based approach to help guide their coverage decisions related to DRDs. The HTA standards used in the evaluation of common diseases, however, are not well suited for assessing DRDs. More specifically, DRDs often fail to meet conventional HTA standards, given the more limited evidence and the higher price points compared with standard therapies due to the rarity of the disease and the small patient population. This means DRDs often receive negative funding recommendations. For instance, CORD estimates that 70% of DRDs receive “Do not list” recommendations from the Common Drug Review (CDR), the national drug review process housed within CADTH.²¹ Negative HTA recommendations make it challenging to be reimbursed by payers, especially public drug plans, and run the risk of precluding or delaying patient access to the treatments that they need. This also raises the following key question: why undertake these assessments in the first place if we already know that most DRDs will not meet the conventional HTA standards?²²

Many academics and stakeholders have acknowledged conventional HTA processes do not work for DRDs and have been calling for an HTA system specifically tailored to DRDs.²³ Some jurisdictions worldwide have also started to explore alternative ways of evaluating DRDs. For instance, in the United Kingdom, the National Institute for Clinical Excellence (NICE) assesses very rare orphan drugs through a specific evaluation committee and based on an interim specific decision-making process.²⁴ The United Kingdom government recognizes that NICE’s standard HTA approach is not suitable for drugs for very rare conditions.²⁵

Other countries have adopted flexible approaches in their HTA process to account for the unique attributes of DRDs. For instance, the Scottish Medicines Consortium (SMC) can choose to accept more uncertainty in the economic case or a higher cost per Quality Adjusted Life Year (QALY) for orphan drugs. Australia’s pharmacare program (PHARMAC) has introduced a “rule of rescue”, which can lead to the funding of certain orphan drugs deemed clinically effective but that have failed the required cost-effectiveness criteria.²⁶

Work is also currently being undertaken at the European Union level to develop a transparent value framework to improve informed appraisal and decision-making on pricing and reimbursement across member states. This process might eventually pave the way to value-based pricing of DRDs in Europe.²⁷

²¹ CORD, *Access for Drugs for Rare Diseases in Canada*, 2014: <http://www.slideshare.net/raredisorders/access-to-drugs-for-rare-diseases-in-canada-april-2014>.

²² Drummond M. et al., *Orphan drugs policies: a suitable case for treatment*, *Eur J Health Econ*, May 2014, 15(4): 335-340: <http://www.ncbi.nlm.nih.gov/pubmed/24435513>.

²³ Hughes-Wilson W. et al., *supra* note 18. See also Drummond M. et al., *supra* note 22; Drummond M., et al., *Assessing the economic challenges posed by orphan drugs*, *Int J Technol Assess Health Care*, 23:1, 2007: <http://www.ncbi.nlm.nih.gov/pubmed/17234015>; and Schlander M. et al., *Incremental cost per quality-adjusted life year gained? The need for alternative methods to evaluate medical interventions for ultra-rare disorders*, *J. Comp. Eff. Res.* (2014) 3(4), 399-422: <http://www.futuremedicine.com/doi/pdf/10.2217/ce.14.34>.

²⁴ Before April 2013, this work had previously been managed by the Advisory Group for National Specialised Services (AGNSS), a national commissioning body, which followed a 12 criteria decision-making framework for ultra orphan drugs. NICE’s interim decision-making framework builds on AGNSS’ work.

²⁵ Highly Specialised Technologies programme: Interim process and methods, May 2013: <http://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/Highly-Specialised-Technologies-Interim-methods-and-process-statements.pdf>.

²⁶ CADTH, *Drugs for Rare Diseases: Evolving Trends in Regulatory and Health Technology Assessment Perspectives*, *Environmental Scan*, October 2013: http://www.cadth.ca/media/pdf/ES0281_RareDiseaseDrugs_es_e.pdf.

²⁷ This is the work of the European Commission’s Working Group on the Mechanisms of Coordinated Access to Orphan Medicinal Products (MoCA). This initiative builds on the framework developed by the Clinical Added Value of Orphan Medicinal Products (CAVOMP). See European Commission, Platform on access to medicines in Europe: http://ec.europa.eu/enterprise/sectors/healthcare/competitiveness/process_on_corporate_responsibility/platform_access/ind

In Canada, in the absence of a national approach for assessing DRDs, Ontario developed a separate seven-step evaluation framework for assessing funding of selected DRDs under its public drug program. This approach is premised on the principle that the level of evidence we can reasonably expect from a new drug depends partly on the potential size of the patient population, which significantly impacts the ability to undertake traditional clinical trials (i.e., double-blind randomized controlled trials).²⁸ Further, while affordability remains a consideration, cost-effectiveness is not a deciding factor in the evaluation.²⁹ New Brunswick recently adopted the same approach as Ontario,³⁰ and Alberta and British Columbia have both introduced programs related to DRD funding.³¹

At the national level, however, in May 2014, CADTH decided against developing a separate process tailored to DRDs, and opted instead to integrate reviews for DRDs into its existing process for evaluating drugs, i.e., the CDR. While CADTH made some slight adjustments to its review process to accommodate DRDs, it will continue to apply conventional HTA standards to DRDs. The slight adjustments made included:³²

- enhanced engagement with outside experts for reviews of orphan drugs
- opportunity for pre-meetings with manufacturers who meet certain criteria determined by CADTH

Similarly, Québec's INESSS has not adopted a specific approach for evaluating DRDs. In 2011, the agency produced an environmental scan, which reviews international practices with regard to DRDs.³³ Québec's Health Minister at the time intended to develop a strategy on DRDs, but this never came to fruition.

HTA organizations, payers, industry and patients in Canada need to work together, and in collaboration with their international counterparts, to develop and implement a **transparent approach to the evaluation of DRDs, which takes into account the unique characteristics of these therapies**. This new approach would benefit the following key stakeholders:³⁴

- **Patients:** It would facilitate patient access to the treatments that they need. A more transparent approach would also help promote accountability in the decision-making.
- **Payers:** An evaluation tool customized to DRDs would help public drug plans and provincial/territorial health ministers make more informed reimbursement decisions on DRDs and better allocate their budgets based on the outcome of these specialized

[ex_en.htm](#); and Morel T. et al., *Reconciling uncertainty of costs and outcomes with the need for access to orphan medicinal products: a comparative study of managed entry agreements across seven European countries*, Orphanet Journal of Rare Diseases, 8:198, 2013: <http://www.ojrd.com/content/pdf/1750-1172-8-198.pdf>.

²⁸ Drummond M. et al., *supra* note 22.

²⁹ *Ontario Public Drug Programs (OPDP) Evaluation Framework for Drugs for Rare Diseases (DRDs)*, presentation deck by McArthur D., former Assistant Deputy Minister and Executive Officer, Ontario Public Drug Programs, October 2010: http://www.health.gov.on.ca/en/pro/programs/drugs/how_drugs_approv/docs/ontario_drd_evaluation_framework.pdf.

³⁰ New Brunswick Government's website:

http://www2.gnb.ca/content/gnb/en/services/services_renderer.201352.New_Brunswick_Drugs_for_Rare_Diseases_Plan.html.

³¹ Alberta established a Rare Disease Drug Program in 2009 and British Columbia's public drug plan has a DRD funding evaluation framework in place. See CADTH, *supra* note 26.

³² CDR Update Issue 103, May 2014: <http://www.cadth.ca/en/products/cdr/cdr-update/cdr-update-103>.

³³ INESSS, *Prise en charge des maladies rares – Expériences étrangères*, ETMIS 2011; Vol. 7 : NO 6: https://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/OrganisationsSoins/ETMIS2011_Vol7_No6.pdf.

³⁴ Hughes-Wilson W. et al., *supra* note 18. Sussex J. et al., *A Pilot Study of Multicriteria Decision Analysis for Valuing Orphan Medicines*, Value in Health, 16 (2013), 1163-1169: <http://www.sciencedirect.com/science/article/pii/S1098301513043568>.

assessments. A transparent HTA approach for DRDs would also allow for a more structured dialogue between payers and stakeholders, and help increase the defensibility of decisions.

- **Industry:** It would foster a more predictable and transparent environment for reimbursement and help stimulate innovation and investment in DRDs.

In developing a new evaluation approach for DRDs, a number of key elements will need to be considered, including those set out below.

A consistent definition

The definition of DRDs used for the purposes of HTA reviews should be aligned with Health Canada's proposed regulatory pathway. According to Health Canada, "[a] rare disease is a life-threatening, seriously debilitating, or serious chronic condition that only affects a very small number of patients (typically less than 5 in 10,000 persons)" and "[o]rphan drugs are those drugs used to treat rare diseases."³⁵

A common definition would facilitate access to the Canadian market and foster collaboration and sharing of information among all those involved in the approval and evaluation or funding of DRDs (i.e., the regulators, HTA agencies and the payers).

Expert involvement

Given the complexity and rarity of orphan diseases, involving experts with real-life experience is essential to properly evaluate DRDs. The HTA process should be able to work through declared conflicts of interest, in order to obtain the best professional advice. The number of clinician specialists in the DRD community for each disease is by nature very limited, and many will have been involved at some point in the development of the product under review. This should not preclude them from acting as expert advisors for the review process. A separate DRD expert committee would also greatly help facilitate reviews.

HTA methodology

Conventional HTA methodology, which typically focuses on clinical and cost-effectiveness evidence and models, present significant challenges for DRDs for the following reasons:³⁶

- DRDs often have higher acquisition costs as R&D investments have to be recouped from a small market worldwide. These acquisition costs impact the cost-effectiveness of DRDs compared to regular treatments, making it impossible, in most circumstances, for DRDs to meet standard cost-effectiveness thresholds.
- The clinical and economic evidence is more limited for DRDs given the rarity of the disease and the small patient population. For instance:
 - Clinical studies are often not as robust as those conducted for standard therapies, as they are often limited by small heterogeneous populations, have short durations of follow-up and there is limited scientific understanding or consensus on clinical endpoints.
 - There is often uncertainty in the estimates of cost-effectiveness due to limited sample sizes and the absence of data on long-term disease progression.

³⁵ Health Canada's website, *supra* note 1.

³⁶ Drummond M., *supra* note 23; and Sussex J. et al., *supra* note 34

Many have argued the focus on clinical and cost-effectiveness is too narrow, especially in the context of DRDs. Assessments of DRDs should be broadened to consider other additional important factors, such as disease severity, patient population size, the availability of other alternatives (i.e., level of unmet medical need), equity of access, the level of impact on the condition offered by the new treatment, budgetary and other practical constraints (such as staff availability), economic impact and evidence quality. There are many other potential criteria reflecting Canadians' collective preferences that could more systematically be included in the evaluation framework. Some have suggested applying a multi-criteria decision analysis (MCDA) process, which enables decision-makers to explicitly trade off various factors against each other. This approach would involve identifying the criteria for assessing the value of each DRD and assigning weights to each of the criteria to determine their relative importance to the reimbursement decision.³⁷

MCDA has often been used to guide decision-making in healthcare, as well as other sectors, such as transportation and social services. In the context of HTA, an expert committee in the United Kingdom for specialized drugs applied an MCDA framework, prior to 2013, when it was taken over by NICE.³⁸ The interim method currently used by NICE's Highly Specialised Technologies evaluation committee builds on this framework and is based on multiple criteria.

As well, the National Health Service of England has essentially proposed an MCDA process for determining which oncology drugs will be funded by the Cancer Drugs Fund.³⁹ The Office for Health Economics (OHE) has also recently piloted a study on MCDA for valuing DRDs and concluded that the piloted approach works, and could be developed for use by payers and HTA agencies.⁴⁰

In Canada, recognizing that evidence is only one consideration, alternative approaches to the traditional HTA framework, which includes multi-factorial decision-making, have been explored and applied in the hospital setting.⁴¹

Patient involvement

Patients offer a range of perspectives positively contributing to the assessment of the value of a treatment. They provide perspectives on the burden of illness, the impact of the disease on their day-to-day life, the most challenging aspects of their condition, unmet medical needs and experience with treatments. This is especially true for patients suffering from rare diseases, as they have often become "experts" in living with their condition, given the lack of available

³⁷ Hughes-Wilson W. et al., *supra* note 18; Sussex J. et al., *supra* note 34; Goetghebeur M. et al., *Combining multicriteria decision analysis, ethics and health technology assessment: applying the EVIDEM decisionmaking framework to growth hormone for Turner syndrome patients*, *Cost Effectiveness and Resource Allocation* 2010, 8:4: <http://www.ncbi.nlm.nih.gov/pubmed/20377888>.

³⁸ The expert committee was the AGNSS, which used to evaluate highly specialized drugs in the United Kingdom before NICE took over in 2013.

³⁹ See Sussex J. et al., *supra* note 34.

⁴⁰ The piloted approach included the following eight attributes: availability of existing treatments, diseases survival prognosis with current standard of care, disease morbidity and patient clinical disability with current standard of care, social impact of disease on patients' and carers' daily lives with current standard of care, treatment innovation, evidence of treatment clinical efficacy and patient clinical outcome, treatment safety and social impact of treatment on patients' and carers' daily lives. It should be noted that the OHE opted to "exclude the net monetary cost impacts of the disease and the treatment, as to include them would require monetary values for all the non-monetary criteria. It sought instead to establish the value of an OMP [orphan medicine product] to set against its net cost impact." See Sussex J. et al., *supra* note 34.

⁴¹ Martin, J., University of Western Ontario, *How to Win Friends & Influence Policy – Stories from the Hospital Perspective*, 2013: http://www.slideshare.net/CADTH_Symposium/a3-how-to-win-friends-and-influence-policy-janet-martin-salon-e.

knowledge and support due to the rarity of the condition. This is why it is crucial for HTA bodies to capture and consider the patient voice in a systematic and robust way when assessing DRDs.

Given the low prevalence of rare diseases, individual patients and caregivers in addition to patient groups should be able to provide input on the drug being reviewed. In this regard, CADTH should consider formalizing and expanding individual patient and caregiver input, which is currently the subject of a pilot project.

Engagement with manufacturers

A continuing two-way dialogue between HTA bodies and manufacturers will lead to stronger reviews resulting in clearer and more informed decision-making by governments. The HTA process for DRDs should allow for opportunities for engagement with manufacturers throughout the review process, and not just through pre-meetings. Manufacturers should be able to present and discuss directly to HTA decision-makers and to subsequently meet with them to address any issues in their initial report prior to the publication of final recommendations.

REIMBURSEMENT

Coverage of DRDs is more restricted than for standard therapies, and there are significant disparities in coverage across the country. This is especially true for public drug plans. The principal reason why payers are usually more reluctant to negotiate and fund DRDs is because of their higher price-per-patient. Payers are also concerned about the increased growth rates of DRDs, and the impact this might have on their future budgets.

While DRDs are often more costly than standard therapies on a per patient basis for reasons previously discussed in this paper, it should be emphasized their budget impact is generally relatively low because of the rarity of the conditions and the small patient populations. Specifically, CORD estimates DRDs represent less than 1% of public drug spend in Canada.⁴² At the international level, in France, which is considered to be at the permissive end of the spectrum with regard to access and reimbursement of DRDs in Europe, it is estimated DRDs still represented a small portion of total drug expenditure in 2013 (i.e., 3.2%).⁴³ Further, studies have shown that fears about unsustainable growth in DRDs expenditure are not justified. A recent study demonstrated the budget impact of DRDs in France and Sweden is expected to plateau between 4% and 5% of the total national drug market spending in 2020, and will therefore remain a small proportion of total drug expenditure.⁴⁴ More specifically, this analysis forecasts the budget impact will slow down starting in 2018 despite continued growth of orphan drugs designations for two reasons: (1) low market approval success rate for DRDs; and (2) savings resulting from generic products replacing existing DRDs will lose their intellectual property protection. Another recent study, which analyzed the budget impact of drugs for ultra-orphan non-oncological diseases in Europe concluded concerns about an uncontrolled growth in

⁴² CORD, *supra* note 21.

⁴³ Hutchings A. et al., *Estimating the budget impact of orphan drugs in Sweden and France 2013-2020*, Orphanet Journal of Rare Diseases 2014, 9:22: <http://www.ojrd.com/content/pdf/1750-1172-9-22.pdf>.

⁴⁴ Hutchings A. et al., *supra* note 43. These countries were examined because Sweden and France respectively are considered to be at the restrictive and permissive ends of the spectrum with regard to DRD accessibility and reimbursement. This study was consistent with a previous study conducted by some of the same authors: see Schey C. et al., *Estimating the budget impact of orphan medicines in Europe: 2010-2020*, Orphanet Journal of Rare Diseases 2011, 6:62: <http://www.ojrd.com/content/pdf/1750-1172-6-62.pdf>.

spending for these treatments is not supported by the evidence.⁴⁵

Mimetogen Pharmaceuticals, with offices in Montreal, is a clinical stage biotechnology company focused on developing novel therapeutic approaches for indications including dry eye disease, glaucoma and other degenerative diseases of the retina, such as retinitis pigmentosa.

In addition to their limited impact on drug budgets, DRDs offer real tangible economic benefits to the healthcare system and contribute to a stronger Canadian economy. For instance, DRDs can reduce overall health care expenditure by replacing or preventing costly health interventions and hospitalization. As well, DRDs lead to improved health outcomes, allowing patients with orphan diseases to live better and longer lives, and participate in the workforce. It is therefore important to go beyond silo budgeting of pharmaceuticals and to consider these important economic benefits when making coverage decisions relating to DRDs.

In recent years, innovative funding approaches relating to DRDs have started to emerge, both within Canada and at the international level. In Canada, private insurers have launched a national drug pooling solution for all insured drug plans, aimed at protecting the plans from the financial impact of high-cost, recurring drug claims.⁴⁶ In Scotland, health boards have opted to pool resources to share the costs and risk of funding high cost, low volume medicines for certain orphan diseases that have been approved by the Scotland's HTA agency, the SMC.⁴⁷ In October 2014, Scotland also announced the establishment of a New Medicines Fund to make new medicines available to people with rare conditions or those at the end of life.⁴⁸ In England, the government has established a Cancer Drugs Fund to cover the costs of certain new oncology drugs that would not have otherwise been available.⁴⁹

More recently, in Canada, provincial governments decided to establish a working group led by Alberta, British Columbia and Ontario.⁵⁰ The group will explore how to manage the cost of DRDs with evidence-based approaches. Although little information has been publicly released on this initiative, it is encouraging provinces recognize the need to work collaboratively on this issue. It is hoped their efforts will lead to a funding approach with more equitable access and enhanced benefits to patients with rare diseases and predictable market conditions for the industry to

⁴⁵ Schlander M. et al., *Budget impact analysis of drugs for ultra-orphan non-oncological diseases in Europe*, Expert Rev. Pharmacoecon. Outcomes Res., 1-9 (2014): <http://www.ncbi.nlm.nih.gov/pubmed/25312018>.

⁴⁶ See Canadian Life and Health Insurance Association's news release, 2012:

http://www.clhia.ca/domino/html/clhia/clhia_lp4w_lnd_webstation.nsf/page/BA0CB8C6EA6A2C70852579D4006739D0.

⁴⁷ National Services Division, Risk Share: <http://www.nsd.scot.nhs.uk/%5C%5C/services/riskshare/index.html#a2>.

⁴⁸ Scottish Government, Press Release, 2014: <http://news.scotland.gov.uk/News/-40m-for-new-medicines-10e4.aspx>.

⁴⁹ See National Health Services (NHS) England: <http://www.england.nhs.uk/ourwork/pe/cdf/>. Through this fund, the government has set aside money to pay for cancer drugs that have not been approved by NICE and that are not available within the NHS in England. This could be because the drugs have not been evaluated yet by NICE or because NICE have recommended they not be reimbursed for clinical or cost-effectiveness reasons. The aim of the fund is to make it easier for people to get as many treatments as possible. See Cancer Research UK: <http://www.cancerresearchuk.org/about-cancer/cancers-in-general/cancer-questions/cancer-drugs-fund>.

⁵⁰ Canadian Intergovernmental Conference Secretariat's Press Release, 2014: <http://www.scics.gc.ca/english/Conferences.asp?a=viewdocument&id=2217>.

attract investment needed to develop these products. In particular, the following key principles should be considered when developing a national approach to funding DRDs:

Universal coverage of DRDs

In order for this approach to work, all governments would have to agree to fund the same DRDs based on the same criteria and within the same timeframe. In addition to coverage, health systems should harmonize clinical practice and guidelines for treatment of DRDs to promote increased consistency across the country.

Aligned with rare disease definition of regulatory pathway

The definition of “rare disease” for the funding approach should be the same as Health Canada’s definition found in its proposed orphan drug framework (i.e., less than 5 in 10,000). Using the same definition and designation for the same medicine would help harmonize the regulatory pathway expected to be established shortly with reimbursement practices, leading to more streamlined and timely access to DRDs.

Timely reimbursement

Governments should strive to adopt an approach aimed at improving the timeframe for reimbursement of DRDs. In particular, health system stakeholders should consider how a new funding approach ties into other national processes, such as the CDR, the pan-Canadian Oncology Drug Review and the pan-Canadian Pharmaceutical Alliance (pCPA), to avoid any duplication in the reimbursement process.

A consistent and accountable mechanism

Clear principles and standardized parameters for this funding approach need to be established, including consistent accounting and costing methodologies. This may take the form of an oversight mandate for an organization, such as an ombudsman or auditor general, to ensure the principles and parameters of the funding model are being consistently applied by all jurisdictions.

A transparent and accountable mechanism

The principles and parameters of the funding model should be shared and discussed with healthcare system stakeholders. This will promote better relationships among payers and stakeholders and foster increased stakeholder trust in this new funding system.

In addition to the cost of DRDs, payers are often concerned about the uncertainty regarding the real-world clinical and economic performance of certain DRDs, given the more limited available evidence for these treatments at product launch. In such cases, rather than denying or delaying reimbursement of DRDs, payers and manufacturers could work together to develop innovative reimbursement solutions.

More specifically, consideration should be given to negotiating, at the pCPA or at the individual provincial level, “managed entry agreements” (MEAs). MEAs include financial-based arrangements, which are already commonly used in Canada and which are aimed at managing budget impact (e.g., discount, price-volume or utilization capping agreements). MEAs may also

include performance-based risk-sharing arrangements, which are being negotiated in a number of European countries and which can be used to either:⁵¹

- address the uncertainty through better evidence collection while a drug is used within a healthcare system (also known as coverage with evidence development);⁵² and/or
- manage real-world utilization and improve the cost-effectiveness of a new drug (e.g., outcomes guarantees, meaning payment for responders only).⁵³

Arrangements focused on coverage with evidence development could involve, for instance, observational studies linked to a patient registry. In such a case, cross-border patient registries, which include patient data across many countries, should be considered to improve the quality of the data collected and avoid the duplication of efforts.⁵⁴

HEALTH SYSTEM ADOPTION

Patients with rare diseases face immense challenges, ranging from correct diagnosis and testing to availability of information on their condition, treatment and appropriate care. This is in part because knowledge about rare diseases, care and treatments are not easily accessible across the Canadian healthcare system, and the care provided to patients is often not sufficiently coordinated.

In Canada, some measures have been taken to help address this gap. As mentioned previously in this paper, CIHR created a Canadian interface with the Orphanet web portal. This portal provides information to patients and healthcare providers on rare diseases and treatments and on resources that are available in Canada (e.g., clinical trials, research projects, etc.).⁵⁵

While this is a positive first step, more needs to be done. One way of increasing the level of knowledge and coordination of care in Canada would be through the establishment of **centres of expertise**. While some centers currently exist for some rare diseases in Canada, they need to be more properly resourced and more of them need to be established to:

- provide **information** adapted to the specific needs of patients and their families and of health and social professionals in partnership with patient organizations
- provide access to appropriate **diagnostic testing**
- provide **comprehensive and expert care** to rare disease patients, drawing on multi-disciplinary competences
- offer **education and training** to healthcare professionals from all specialties to provide adapted care to rare disease patients and their families
- **raise awareness** of the diseases and available treatments

Further, governments might want to explore the idea of establishing a national rare disease office to help coordinate these centres of expertise in order to foster exchange of information and best practices among them and to refer patients and healthcare professionals to the appropriate place. A national office could also be tasked with conducting national rare disease surveillance and coordinating research for rare diseases. Of note, Ireland recently adopted its

⁵¹ Morel T. et al., *supra* note 27.

⁵² This is a scheme at the population level.

⁵³ This is a scheme at the patient level.

⁵⁴ Morel T. et al., *supra* note 27.

⁵⁵ Orphanet website Canadian entry point: <http://www.orpha.net/national/CA-EN/index/homepage/>.

national rare disease plan,⁵⁶ which calls for a national office for rare diseases. European reference networks have also been established to help centres and health professionals across Europe exchange information and to coordinate specialized care for patients.⁵⁷

Finally, any national rare disease office would need to tie into international networks for rare diseases to ensure appropriate pooling of resources and expertise across national borders, thereby streamlining and facilitating timely decision making.

Shire, which has offices in Montreal, is a biotechnology company that develops and markets medicines for rare diseases. The company has ongoing research projects including hereditary angioedema, ACE inhibitor-induced angioedema, Fabry disease, Hunter syndrome, retinopathy of prematurity, and Alagille syndrome. Shire recently acquired NPS Pharmaceuticals, which has its Canadian headquarters in Pointe Claire, Quebec. The company's current key therapeutic areas are gastrointestinal disease and endocrine disorders. These include: short bowel syndrome, hypoparathyroidism, and autosomal dominant hypocalcemia.

⁵⁶ Ireland's Department of Health, *National Rare Diseases Plan for Ireland 2014-2015*: <http://health.gov.ie/wp-content/uploads/2014/07/EditedFile.pdf>. In 2009, the EU has recommended that member countries establish and implement plans to combat rare diseases by the end of 2013. See European Commission, Rare Diseases: http://ec.europa.eu/health/rare_diseases/national_plans/index_en.htm.

⁵⁷ European Commission, European Reference Networks: http://ec.europa.eu/health/ern/policy/index_en.htm.

TABLE 1: DEFINITIONS OF RARE DISEASE IN OTHER JURISDICTIONS

Jurisdiction	Legislative source	Definition
<p>European Union European Medicines Agency (EMA)</p>	<p><i>Regulation EC No. 141/2000</i></p>	<p>A condition affecting not more than 5 in 10,000 persons in the European Union</p> <p>It should be noted that to qualify for <u>orphan designation</u>, a medicine must meet a number of criteria:</p> <ul style="list-style-type: none"> • it must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating • the prevalence of the condition in the European Union must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development • no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition
<p>United States (FDA)</p>	<p><i>Orphan Drug Act (as amended), 21 U.S.C. 316</i></p>	<p>A disease or condition that affects fewer than 200,000 people in the United States</p> <p>It should be noted that to obtain <u>orphan designation</u>, drugs must meet the following criteria:</p> <ul style="list-style-type: none"> • drugs and biologics intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the U.S., or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug

Japan		<i>Pharmaceutical Affairs Law 145</i>	<p>A disease that affects fewer than 50,000 patients in Japan</p> <p>Conditions for to obtain <u>orphan designation</u> include:</p> <ul style="list-style-type: none"> • potential target patient population of less than 50,000 • no alternative drugs or treatments are available or the product is a significant improvement in efficacy or safety compared with current therapies • a high probability of development success
Australia		<i>Therapeutic Goods Regulations, 1990, S.R. No. 394, Part 3B (Orphan Drugs)</i>	<p>A disease, or condition, likely to affect not more than 2,000 individuals in Australia at any time</p> <p>Another alternative criterion which leads to orphan designation consists of a drug that is not commercially viable</p>
Taiwan		<i>Rare Disease Control and Orphan Drug Act</i>	<p>A disease or condition that affects fewer than 1 in 10,000 people, has a genetic origin and is difficult to treat</p>

TABLE 2: COMPARISON OF REGULATORY AND ECONOMIC INCENTIVES ACROSS JURISDICTIONS

Jurisdiction	Market Exclusivity	Accelerated Review Availability	Scientific advice ⁵⁸	Fee Reduction/Waiver for Market Authorization Application	Financial Incentives
European Union	10 years - can be extended by 2 years for products that also have complied with an agreed pediatric investigation plan and can be reduced to 6 years where the product is sufficiently profitable	Yes	Yes	<p>Yes</p> <p>Also includes reduced fees for protocol assistance, inspections before authorisation and applications for changes to marketing authorisations made after</p>	<p>Tax credits developed by member states</p> <p>Research grants by member states and by European Commission</p>

⁵⁸ Includes protocol assistance and/or development consultation.

Jurisdiction	Market Exclusivity	Accelerated Review Availability	Scientific advice ⁵⁸	Fee Reduction/Waiver for Market Authorization Application	Financial Incentives	
	Prevents similar products from being approved for the same indication unless a second product is safer, more effective or clinically superior			approval, and reduced annual fees		

Jurisdiction	Market Exclusivity	Accelerated Review Availability	Scientific advice ⁵⁸	Fee Reduction/Waiver for Market Authorization Application	Financial Incentives
United States	7 years - can be extended by 6 months for pediatric drugs Prevents same product being approved for the same indication unless clinical superiority is shown	Yes	Yes	Yes	The FDA provides clinical research funding through the Orphan Products Grants Program 50% federal tax credit for clinical research
Japan	10 years During this period, no other applicants with the same medicinal products can submit an application for a market authorization for the same active substance	Yes	Yes	Yes	Subsidies of up to 50% to offset clinical and non-clinical development costs Tax Exemption Law 12% of expenses (not including grant subsidies)
Australia	5 years (same as other non-orphan drugs)	Yes	Yes	Yes	No
Taiwan	10 years During this period, no applications for registration and market approval of pharmaceuticals of the same kind will be approved unless clinical superiority is shown or if the price of the first DRD (with market authorization) is unreasonable	Yes	Yes	Yes	Yes Financial subsidies for local R&D and awards to special contributors from the central regulatory authority

Table based on Franco, P., *Orphan drugs: the regulatory environment*, Drug Discovery Today, Vol. 18, Numbers 3/4, February 2013; CADTH, *Drugs for Rare Diseases: Evolving Trends in Regulatory and Health Technology Assessment Perspectives*, Environmental Scan, October 2013: http://www.cadth.ca/media/pdf/ES0281_RareDiseaseDrugs_es_e.pdf and Peipei Song et

al., *Rare diseases, orphan drugs, and their regulation in Asia: Current status and future perspectives*, (2012) *Intractable & Rare Diseases Research* 1(1):3-9:
<http://www.irjournal.com/action/downloadaddoc.php?docid=511>.

van Weely S. et al., *Background Paper 6.19 Rare Diseases*, March 2013: http://www.who.int/medicines/areas/priority_medicines/BP6_19Rare.pdf.