
Canada's Orphan Drug Framework: Lessons from the United States, Europe and Japan

Westerly Luth¹ MSc, Sarah Ali-Khan² PhD and Tania Bubela¹ PhD JD

1. School of Public Health, University of Alberta

2. Centre for Intellectual Property Policy (CIPP), Faculty of Law, McGill University

Introduction

Canada is in the process of developing an orphan drug regulatory framework (the “Canadian Framework”)¹ in which an orphan drug is defined as one targeting a disease that affects fewer than 5 in 10,000 Canadians. The federal government announced the development of the Canadian Framework in 2012. Health Canada has held workshops and announced pilot projects related to the Canadian Framework, but as of 2015, the Minister of Health still has not approved the Canadian Framework.

Here, we analyse lessons that may be learned from the implementation and operation of orphan drug frameworks in the United States of America (US), Japan, and the European Union (EU). Such frameworks aim to create incentives for the pharmaceutical industry to develop treatments for rare diseases. We compare frameworks across these jurisdictions to identify similarities and differences with the proposed Canadian Framework and to highlight problems that may be expected based.

Background

The original rationale behind orphan drug frameworks is that, for small patient populations, the cost of drug research and development (R&D) is likely to exceed product revenues, based on the prices payers were willing to pay for conventional drugs at the time. Under this set of assumptions, R&D for orphan drugs is therefore not an attractive economic proposition for pharmaceutical and biotechnology companies. Under pressure from patients and their advocates, policy makers in some countries have developed orphan drug frameworks that offer a suite of incentives for pharmaceutical companies to prioritize the development of drugs to treat rare diseases. The goal of

these frameworks is to increase patient access to treatments that would otherwise fail to be developed because of the absence of market forces. The US was the first to legislate in 1983 with the *Orphan Drug Act*², which has since served as a template for other jurisdictions. Japan implemented its *Orphan Drug Regulation* in 1993³ and the EU passed *Regulation (CE) N°141/2000*⁴ in 2000. In contrast, Canada only moved to draft the Canadian Framework in December 2012¹. As such, Canada has an opportunity to learn from the experiences of other jurisdictions.

Orphan drug frameworks (legislative or regulatory) provide a variety of incentives to encourage pharmaceutical companies to develop treatments specifically for rare diseases. Administrative authorities in each jurisdiction supervise the implementation and oversee the operation of these frameworks. In all jurisdictions, a company must first apply for an orphan drug designation for its product in order to access incentives. The financial incentives designed to reduce development costs include: tax credits for clinical trial expenses, research grants from funding agencies, and waived administrative fees for regulatory approvals. In the jurisdictions we reviewed, orphan drugs are also eligible for priority regulatory approval programs such as the FDA Fast Track program in the US, which allows for expedited approval for drugs that treat serious conditions and fill unmet medical need⁵. Companies also access additional advice and assistance on technical matters during drug development and approval, beyond that available for non-orphan drug developers. Once an orphan drug is released to market for a specific indication, it is granted market exclusivity for use in that indication, which protects it from direct competition for 7-10 years depending on the jurisdiction (see Table 1)⁶. Collectively, these incentives aim to reduce the cost of developing and marketing orphan drugs and to delay direct competition from generics once on the market. Table 1 summarizes the characteristics of different orphan drug frameworks in different jurisdictions. Canadian information is based on the proposed orphan drug framework released in 2012 and applicable existing legislation/regulations.

Table 1. Comparison of International Frameworks for Orphan Drugs.

	United States of America ⁷	European Union ⁷	Japan ⁷	Canada (proposed and existing) ¹
Orphan drug framework	<i>Orphan Drug Act</i> (1983)	<i>Regulation (CE) N°141/2000</i> (2000)	<i>Orphan Drug Regulation</i> (1993)	Initial draft Discussion Document
Administrative authority	FDA ^a / OOPD ^b	EMA ^a / COMP ^d	MHLW ^e /OPSR (Orphan Drug Division)	Health Canada
Threshold prevalence of the targeted disease (per 10,000 individuals)	7.5	5	4	5
Additional non-prevalence conditions for ‘orphan drug’ designation		Intended to treat life-threatening or chronically debilitating diseases; meets an unmet need or provides significant benefit to patient compared to existing therapy.	Meets an unmet need or is safer and/or more effective than existing alternatives; must have high probability for successful development with theoretical justification for efficacy in treating a rare disease	Provides potentially substantial benefit for the patient compared to existing therapy
Alternative non-prevalence definitions for “orphan drugs”	Alternatively: treats a disease affecting more than 7.5/10 000 individuals for which there is no reasonable expectation of recovering R&D costs via sales	Treats a disease affecting more than 5/10 000 individuals for which there is no reasonable expectation of recovering R&D costs via sales		
Market exclusivity	7 years	10 years	10 years	8 years (for all innovative drugs*)

Tax credit	Yes: 50% for clinical studies	Managed by the member states	Yes: 6% for any type of study & limited to 10% of the company's corporation tax	No
Grants for research	National Institutes of Health (NIH), Orphan Products Grants Program ⁸	Horizon 2020, E-Rare, International Rare Diseases Consortium ⁹	Drug Fund for Side-Effects Relief and Research Promotion, Small Business Innovation Research ¹⁰	Canadian Institute for Health Research
Reconsideration of applications for orphan designation	No	Yes (every 6 years)	Yes	Yes
Technical assistance for elaboration of the application file	Yes	Yes	Yes	Yes
Accelerated marketing procedure	Yes	Yes	Yes	Yes
<p>a. FDA: Food and Drug Administration b. OOPD: Office of Orphan Products and Development c. EMEA: European Agency for the Evaluation of Medicinal Products d. COMP: Committee for Orphan Medicinal Products e. MHLW: Ministry of Health, Labour and Welfare * See below, Lesson 5. Intellectual Property Incentives for Orphan Drugs, for more discussion.</p>				

Lessons for Canada’s Orphan Drug Framework

This section outlines lessons for Canada’s Orphan Drug Framework based on a qualitative analysis of key issues raised in the academic literature on the implementation and operation of orphan drug frameworks, internationally (see Appendix 1 for details of our Analytical Approach). Discussed below are the key lessons that fell within the following four categories of issues:

1. Clarity in definitions of orphan drugs;

2. Orphan drugs that become highly profitable;
3. Problems with orphan drug clinical trial design; and
4. Internationally inconsistent funding incentives and guidance following orphan drug designation.

1. Clear definition of orphan drug

The problem with a disease prevalence-based definition for orphan drugs

All reviewed frameworks use disease prevalence-based definitions as the baseline criteria to target economic incentives. In addition, jurisdictions allow additional justifications or specify further criteria be met, thus augmenting the scope and stringency of policy across different settings.

A range of prevalence cut-offs is employed across jurisdictions (Table 1). In the EU, orphan drugs must meet a prevalence cut off and also treat a life threatening or chronically debilitating disease³. In the US, applicants can rely on prevalence, or they can make the case that the expected return on investment for the drug is low². In Japan, an orphan drug must have a theoretical rationale for its use in treating an orphan disease, a high probability of successful development, and in addition, address an unmet or underserved medical need³.

However, prevalence-based definitions are not grounded in epidemiological rationales. Their fit-to-purpose is challenged by advances in molecular testing that are re-defining existing disease taxonomies and calling into question the 'rarity' of some indications^{11, 12}. The current focus on personalized medicine is also increasing delineations between patient groups, thereby creating ever more rare disease classifications^{12, 13}. For example, in some cases multiple rare disease classifications have been created from a single common disease. In these circumstances, all the new 'rare' diseases have the same shared R&D cost base, but they are being presented as separate diseases by companies in order to qualify for orphan drug incentives. Because the drugs have a common R&D cost base, they would have been developed in the absence of orphan

drug incentives. Thus, companies are abusing the system by accessing incentives without providing societal benefit in the form of novel therapies. As such, advances in medical definitions of disease make the use of prevalence-based definitions in orphan drug frameworks increasingly problematic for identifying the diseases that should qualify for orphan drug incentive.

A further challenge to prevalence definitions is that they have the potential to be exploited by companies to acquire orphan status for many similar indications for a single drug¹⁴. Called ‘salami slicing’, use of this drug development strategy may enable companies to target rare subsets of common diseases¹⁵ to acquire orphan status for many similar indications for a single drug¹⁴. In doing so, companies can profit from a larger patient population while retaining orphan drug incentives, but without providing a commensurate increase in patient access to rare disease treatments. Strategic marketing for different indications for the same drug is a related concern. If a drug is indicated for both a rare and a common disease, there is a financial incentive for companies to bring the rare disease drug to market first, in order to take advantage of orphan drug incentives. This situation results in delayed access and loss of health for patients with the common disease, with the broader economic impact of decreased population health. Reliance on prevalence definitions will encourage companies to use profit-maximizing strategies that may poorly serve patients.

Regulatory responses to definitional problems

In response to the concern that pharmaceutical companies are developing drugs for common diseases under the guise of developing drugs for a rare subset of a common disease, the FDA proposed new requirements. Companies must now justify that an orphan drug developed for a rare subset of a common disease is scientifically or medically inappropriate to treat the common disease². The FDA also clarified that orphan subsets cannot be based on: clinical trial eligibility, sponsor focus on a select indication, specific grade/stages of a disease, or price². Nevertheless, critics have noted that the potential for information asymmetries between companies and regulatory bodies

remains. Thus, companies can exploit these asymmetries to maximize their access to orphan drug incentives¹⁶.

The Canadian Context

The Canadian Framework's definition of an orphan drug is:

- 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 therapy¹.*

This definition emulates those found in other orphan drug frameworks; it combines prevalence, disease severity, and novelty or substantial increased benefit. There are, however, some issues with the proposed definition. Difficulties in defining qualitative measures such as 'substantial' have made other aspects of orphan drug legislation, such as the EU's right to revoke orphan drug designations for 'sufficiently profitable' drugs, unusable. Further, it allows the possibility for existing, already approved drugs, to qualify for orphan drug incentives if they were found to have benefits for patients with orphan indications distinguishable from existing therapies. This has the effect of incentivizing clinical trials to test the efficacy of currently available drugs for orphan indications. This could be problematic if companies seek out drugs with well-established, widely used off-license indications for rare diseases. In these circumstances a company could take advantage of orphan drug incentives while running very low risk trials, and remarket the drug at a higher price for the orphan indication¹⁷. The result would be higher costs for payers and decreased patient access. For example, after colchicine received an orphan designation for familial Mediterranean fever, the price for this formerly generic drug rose from 9 cents per dose to nearly 5 dollars. The company that received market exclusivity for this orphan usage also took legal action to prevent

competitors from manufacturing generic colchicine, which lead to adverse consequences in the form of increased costs to payers and reduced adherence among patients using colchicine¹⁸. The proposed Canadian Framework does not include measures to prevent pharmaceutical companies from charging premium prices for former generics turned orphan drugs. We address the issue of highly profitable orphan drugs in greater detail in the next section.

Canada's Framework will also allow for approval of orphan drugs based on foreign designations¹, a strategy that has been previously recommended¹⁹ and that aims to reduce costs for companies and accelerate patient access. However, because there is no harmonization in orphan drug definitions across jurisdictions, Canada's unique definition may instead increase the burden of evidence required of companies and discourage them from seeking approval in Canada.

2. Addressing highly profitable orphan drugs

Highly profitable orphan drugs

Originally, orphan drug frameworks were introduced because treatments for rare diseases were seen as unprofitable. Contrary to this expectation, some orphan drugs may earn substantial profits. Perhaps naïvely, the creators of orphan drug frameworks did not expect companies to set orphan drug prices any higher than those for non-orphan drugs. However, companies are generally pricing orphan drugs at significantly higher points than conventional drugs^{17, 20}. Thus, some are generating substantial profits despite their small patient populations. The presumption motivating the establishment of orphan drug frameworks is that the development of these drugs is not economically feasible. However, the high profits earned by some orphan drugs suggest that orphan drug provisions are unnecessary, and call into question the justice of public support of orphan drug development as compared to conventional drugs. However, it is difficult to predict whether a drug will become highly profitable, so if orphan drug incentives are maintained, *post hoc* mechanisms may be best suited to recoup needless public

investments in R&D. Another proposal that would avoid setting inappropriate targets for incentives all together, is to base orphan designation on potential health impact rather than on more open-ended prevalence criteria¹². This strategy however, may also face complications.

Responding to highly profitable orphan drugs

The US has no mechanisms to address highly profitable orphan drugs. EU regulators, on the other hand, can revoke an orphan drug designation after 5 years if the orphan drug is ‘sufficiently profitable’. However, due to difficulties defining ‘sufficiently profitable’, the EU has never used this power²¹. In Japan, companies pay a 1% sales tax on orphan drugs with annual profits greater than 100 million yen until they repay Japanese government subsidies²². Thus, only the Japanese model actually addresses the issue of profitable orphan drugs.

The Canadian context

The Canadian Framework does not provide a mechanism to reclaim subsidies. It does not specify the right to review a company’s income from an orphan drug¹, and the only provision for the Minister of Health to revoke orphan status is in the case that the drug no longer meets the orphan drug definition¹. Canada may wish to consider implementing a model similar to Japan’s. However, Canada is a relatively small market. Japan spent \$111 billion USD in 2012, whereas Canada only spent \$22 billion USD on medicines²³. Allowing the possibility to earn higher relative profits than other jurisdictions may be a necessary concession to encourage companies to seek orphan drug designation in Canada that others have previously suggested²⁴.

3. Problems with orphan drug clinical trial design

Clinical trial design issues

Two issues contribute to the inadequacy of risk assessment in orphan drug clinical trials. First, because rare disease populations are small, companies struggle to recruit patients

for orphan drug clinical trials. This small trial size results in reduced power to identify rare risks²⁵. One-third of the clinical trials for orphan drugs approved in the EU had fewer than 100 patients, and half had between 100 and 200 patients²⁶. For some orphan drugs, small clinical trials are justifiable, based on the very small potential patient populations from which to pull participants. Joppi et al.²⁶ argue that in some cases, such as eltrombopag and romiplostim – which were investigated in about 150 patients out of at least 50,000 potential cases of chronic immune thrombocytopenic purpura – there were sufficient potential cases to support a much larger, better powered clinical trial²⁶. Second, clinical trials for orphan drugs are often of short duration relative to the natural history of the condition, thereby under-representing long-term risks of side effects associated with the therapy²⁶. Finally, the strategic misuse by companies of placebo comparators, rather than available treatments to establish clinical superiority, may overstate the benefits of orphan drugs²⁶. These challenges are not exclusive to orphan drugs. However, given that orphan drugs are often approved based on less stringent requirements than conventional drugs, they may in combination act to further weaken the evidence base which regulators use to make benefit-risk evaluations.

Regulatory challenges represented by clinical trial design issues

Despite weaknesses in the evidence for many orphan drugs, the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) continue to approve orphan drugs. The FDA requires two Phase III clinical trials for regular non-orphan drugs¹⁸, but approves orphan drugs with fewer and smaller clinical trials. Nevertheless, orphan drug approval based on clinical trials with small sample sizes raises efficacy and safety concerns^{19,27}. Given that orphan drugs are designed to address unmet health needs, these safety concerns need to be considered in context of risk/benefit balance during approval.

Regulatory responses to clinical trial design issues

The EMA and FDA have mechanisms to address the safety risk posed by orphan drugs. As a condition of approval, the EMA and FDA can mandate post-marketing surveillance^{28, 29}. The FDA and EMA also offer guidance on novel clinical trial designs and statistical methods to improve the evidence generated from orphan drug clinical trials. In the EU, this has been associated with higher approval success rates, shorter assessment times and fewer major objections during review³⁰. In 2011 the FDA promised additional guidelines on adaptive clinical trial designs and statistical methods³¹, and in 2015 the FDA released a draft guidance document for comment³².

Canada's response to clinical trial design issues

The Canadian Framework relies on existing legislation in the Food and Drug Regulations with unspecified minor modifications to address clinical trial design issues¹. Scientific and clinical protocol advice will be available to companies during drug development¹. The Canadian Framework also requires sponsors to report adverse drug effects; report new information pertaining to the benefits, harms, or uncertainties of the orphan drug; develop a detailed post-marketing approval plan to monitor benefits, risks, and uncertainties; and monitor changes to the orphan drug's regulatory status in other countries¹. In the Canadian Framework, Health Canada can also request additional information on a specific orphan drug; require sponsors to compile information on the benefits, risks, and uncertainties of their orphan drug; reassess the orphan drug; stop sales; and suspend or cancel market authorization¹. Aside from Canadian Framework, the Protecting Canadians from Unsafe Drugs Act, known as Vanessa's Law³³ amended the Food and Drugs Act to give Health Canada additional powers to detain products, dispose of products, stop-sales, or recall products after market authorization has been granted.

Prior to the introduction of Vanessa's Law, Canada lacked structures to effectively engage in post-market surveillance activities³⁴. Studies indicate that only a minority of

companies tasked with post-marketing surveillance as part of conditional approval of a product in Canada between 1998 and 2012 had met their commitments in a timely manner³⁵. Indeed, some companies took between 6 and 11 years to fulfil their post-marketing commitments³⁵ by which point many drugs would be at the end of their patent life. Once the drug no longer benefits from market exclusivity, competition from generics reduces incentives for the company to complete its post-marketing commitments (see Lesson 5. Intellectual Property Incentives for Orphan Drugs for further discussion of patents issues with orphan drugs). In fact, in 2011 the Auditor General reported that 25 of 54 safety recommendations Health Canada issued in response to potential safety issues were based on the actions of foreign regulators³⁴. The measures proposed in the Canadian Framework should improve the safety of orphan drugs on the market. However, they also impose significant costs on the companies by making them responsible for post-marketing surveillance. When considered in combination with Canada's relatively small pharmaceutical market, this may discourage companies from marketing their orphan drugs in this country. Instead Canada could benefit from establishing post-market surveillance collaborations with other jurisdictions to identify rare adverse events. These arrangements are being developed between Canada and the US and Canada and the EU. Health Canada and the FDA also jointly launched the Common Electronic Submission Gateway in January 2014, which allows pharmaceutical companies to submit applications to both regulators securely over the Internet³⁶. Since 2003, Health Canada and the FDA have had a confidentiality agreement that allows the agencies to legally share non-public information on products they regulate as part of their cooperative enforcement or cooperative regulatory activities³⁷. Health Canada and the EMA also have a confidentiality agreement, which allows them to exchange information on pre and post-authorization applications³⁸. While the agreements are in place, such international efforts require functional post-market surveillance, which Canada is still developing, and international information-sharing structures in Canada and partner countries³⁹.

4. Inconsistent funding and guidance following orphan drug designation

Financial supports: double dipping concerns

Regulators across jurisdictions with orphan drug frameworks rarely include a check for funding from other jurisdictions as they assess orphan drug applications. The FDA does not check for financial support from other jurisdictions. The EU only requires companies to provide details of grants, tax incentives, or other cost-recovery provisions if they pursue an orphan drug designation based on a low expected return on investment⁴⁰. However, nearly all companies apply for orphan drug designation based on prevalence-based criteria⁴¹, so the EU, in effect, does not check existing financial support.

Though international tax credit abuses are possible, they are not a concern that was articulated in the literature that we reviewed. Companies would have to run multiple clinical trials for the same indication in different jurisdictions to qualify for additional tax credits. However, multiple clinical trials are expensive and do not increase the likelihood of approval¹⁸. Indeed, the FDA and EMA regularly approve orphan drug applications with only one clinical trial¹⁸. The high cost of multiple clinical trials outweighs the benefit of additional tax credits, minimizing the potential for such tax credit abuses by pharmaceutical developers.

Regulatory guidance

Orphan drug frameworks also provide for access to expert advice from regulators during the approval process. The EMA offers companies with a designated orphan drug scientific advice and protocol advice on questions concerning quality, clinical and non-clinical aspects of the application, and the interpretation and implementation of EU guidelines⁴². In the US, companies do not receive scientific or technical advice under the *Orphan Drug Act*, however, orphan drugs do qualify for scientific advice under the FDA's Fast Track process⁵. Many companies access these services to maximize their potential for market approval.

Canadian support and guidance

The Canadian Framework does provide for scientific and clinical protocol advice, and suggests an element of negotiation absent from other orphan drug frameworks: “an application for written regulatory advice ... 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”¹. However, the Canadian Framework lacks specific tax incentives to promote orphan drug clinical trials in Canada¹, although there are fee reductions for small-to-medium enterprises in the Canadian Framework¹. The absence of tax incentives in Canada removes an inducement for companies to develop orphan drugs in Canada.

5. Intellectual Property Incentives for Orphan Drugs

International frameworks also provide additional intellectual property (IP) incentives for orphan drug developers. Here we first discuss intellectual property incentives for regular drugs and then discuss how the intellectual property incentives for orphan drugs augment these.

Patent exclusivity: US patent law gives inventors 20 years of exclusive rights to produce, use, or sell their patented invention⁴³. However, the extensive R&D process for new drugs and FDA review times often reduce the effective patent life of new drugs by 7 to 9 years, though patent term extensions can compensate for this reduction⁴³. The US limits such extensions to 5 years and effective post-approval patent protection to 14 years⁴³. These extensions are available to the developers of all drugs, granting companies market exclusivity to generate a return on investment.

Data exclusivity: Data exclusivity rules also protect US pharmaceutical companies. These provisions preclude the use of the original innovator’s data in the applications of competing follow-on drugs (generics or biosimilars – defined below) made to the FDA⁴³. During the data exclusivity period, generic drug developers must generate on their own preclinical and clinical data for their applications. After the data exclusivity period,

competitors only have to demonstrate bioequivalence with the original drug for FDA approval. Data exclusivity protects drug inventors by delaying the onset of competition, so innovative companies can maximize their profits before alternatives come to market.

Market exclusivity for orphan drugs: In addition to the above mechanisms that are available for all drugs that meet patent criteria, orphan drug frameworks may provide additional intellectual property protection in the form of market exclusivity. For 7 years after the date of the FDA's approval of the orphan drug, the FDA will not approve an application from a different manufacturer for the same orphan drug and indication, with certain exceptions⁴³. The EU and Japan both provide 10 years of marketing exclusivity to orphan drugs⁴³. Competing companies can submit applications for the same product to treat other indications⁴³. Market exclusivity reduces the cost and risk of infringement litigation for companies⁴³. Market exclusivity also fits better with the life cycle of pharmaceutical products because it begins when the orphan drug is approved⁴³. Orphan drug market exclusivity typically adds 0.8 years of protection from competition⁴⁴; these provisions have been credited as the key driver for increases in new orphan drug development in the US⁴⁵.

Problems with intellectual property incentives

Market exclusivity creates some challenges for patients alongside numerous benefits. Policy makers may be swayed to maintain market exclusivity by very vocal support for market exclusivity among pharmaceutical companies to the detriment of other stakeholders whose interests are less well represented⁴⁶. It may also act to limit access to generic options for orphan drugs and, by granting monopolies, reduce competition and innovation⁴⁷. Generic competition is desirable for health systems because it increases patient access by providing lower cost alternatives to brand name innovator drugs.

Biological medicinal products (biologics – defined in Canada as a drug manufactured from or through the use of animals or microorganisms listed in Schedule D to the Food

and Drugs Act⁴⁸) are a subset of orphan drugs with unique intellectual property protections. Partially because of their mode of manufacture in living systems, they tend to be large, complex molecules that are technically challenging to develop and produce. For this reason the US grants novel biologics 12 years of exclusive use, in addition to any orphan drug-associated market exclusivity, to incentivise their development. Biologics are also most often highly priced. Thus, to encourage lower priced alternatives while still granting the original inventor a significant commercial advantage, the US allows the first biologic determined to be interchangeable with the pioneer drug (known as a biosimilar – see discussion below) to receive exclusive use protection for 12 to 42 months⁴³. These protections delay the onset of competition, thereby encouraging innovation by mitigating the inventor and the first biosimilar producers' loss of profits⁴³.

Canadian intellectual property incentives pertaining to orphan drugs

For all innovative drugs (“a drug that contains a medicinal ingredient not previously approved in a drug by the Minister and that is not a variation of a previously approved medicinal ingredient such as a salt, ester, enantiomer, solvate or polymorph”)⁴⁸, Canada provides six years of data exclusivity and eight years of marketing exclusivity from the date of notice of compliance to the innovative drug sponsor under the *Food and Drug Regulations*⁴⁸. Under the *Patent Act*⁴⁹, sponsors have 20 years of patent protection from time of filing, but at the time of writing there are no patent term restorations or extensions in Canada³. The Canadian Framework does not add additional intellectual property incentives for orphan drugs¹.

6. Cost and Availability of Drugs for Rare Diseases

In addition to orphan drug frameworks that incentivise R&D, additional issues may limit access for Canadian patients with rare diseases to orphan drugs. In this section, we first discuss issues raised by the market entry of generic biologics. Finally, streamlined regulatory approvals and incentives for R&D only improve timelines and likelihood for market authorization, they do not influence the market *per se*. It is therefore important to

consider how health system payers (public and private) and, in some cases individuals, will be able to afford the high cost of orphan drugs. We therefore conclude this document with a discussion of the reimbursement landscape.

1. Challenges to regulatory assessment of biosimilarity

Difficulties assessing biosimilarity

Biosimilars – generic versions of an original biological medicine (biologic) – are set to become an increasingly important element in the rare disease therapeutic landscape as patents over pioneer biologics expire⁵⁰. However, regulatory assessment of biosimilarity is challenging and has slowed market entry of biosimilars⁵¹. The FDA approves conventional generic pharmaceuticals on the basis of bioequivalence – the demonstration of equivalent effects on the body in the same dose as a reference product. Biosimilarity is a comparable measure of the safety and potency of a generic biological medicinal product (biosimilar) relative to the original⁴³. Biosimilars must also demonstrate that they are interchangeable with the original biologic⁴³. However, biosimilarity and interchangeability are difficult to prove because the relationship between the structure and function of these complex molecules is poorly understood. This scientific uncertainty is a barrier to the market entry of biosimilars. On the flip side, the complexity of biologics can limit an innovative company's ability to support broad patent claims, allowing competitors to design around the original product. As such, the enforcement of biologic patents is less certain and successful than conventional drug patents⁴⁶.

In the US, non-clinical and clinical data are required to prove biosimilarity and equivalence⁴⁷. In the EU, companies must do comparability studies to prove biosimilarity. European regulators also require clinical trial data to support the safety, effectiveness, and immunogenicity of the biosimilar. For chronic conditions, the EMA also requires immunogenicity data for one year of treatment prior to authorization⁵². Thus, proving biosimilarity is difficult and expensive.

Regulations as hurdles for biosimilar development

The regulatory requirements to demonstrate biosimilarity and interchangeability increase the cost and time necessary to develop biosimilars⁴⁶. Therefore, biosimilars are more expensive than conventional generics to produce and only large companies capable of absorbing significant upfront costs can develop biosimilars⁴⁷.

Canada's biosimilar policy

In Canada, biosimilars are not considered innovative drugs⁵³. Therefore, biosimilars cannot qualify for data protection⁴³. Furthermore, all regulatory restrictions regarding data protection awarded to the original innovative product apply⁴³. In Canada, companies must complete a new drug submission for biosimilars, but they can submit reduced non-clinical and clinical evidence⁴³. However, companies may only seek approval for biosimilars 6 years after the original innovative biologic approval⁴³. Canada's stance on biosimilars differs from other jurisdictions and may ultimately limit the availability of these lower cost alternatives in this country.

2. Uncertain reimbursement and patient access to orphan drugs

Reimbursement for expensive orphan drugs: the EU and US

Pharmaceutical companies strive to maximize the profits generated by orphan drugs. Market exclusivity provides an essential monopoly, encouraging companies to set the highest prices the market will bear²¹ and as a result, orphan drugs have higher prices than conventional drugs¹⁷. Furthermore, payers have limited negotiating power because there are rarely alternative therapies for orphan drug indications⁵⁴. The high cost of orphan drugs is a substantial burden to healthcare payers and their reimbursement decisions can have far-reaching consequences for the care of patients with rare diseases.

EU member countries have different pricing and reimbursement policies. Some countries, like Belgium, Greece, and Italy, impose price controls on orphan drugs²¹.

Germany uses free market drug pricing and has higher prices for orphan drugs than countries like Portugal or Spain, which regulate orphan drug prices²¹. Other countries negotiate lower prices with manufacturers after comparing the price requested by a manufacturer to the price set in other countries²¹. In the EU, a patient's access to orphan drugs depends on where he or she lives.

Unlike the EU countries with national healthcare systems, the US healthcare system has many different payers. The majority of orphan drugs have complete or high rates of coverage among stand-alone drug plans⁵⁵. However, in 2010 stand-alone Medicare Part D prescription drug plans did not cover the orphan drugs clofazimine (Lamprene); glutamine (Nutre-store); zinc acetate (Galzin); and citric acid, glucono-delta-lactone, and magnesium carbonate (Renacidin Irrigation) at all and generics were largely unavailable for orphan drugs that many stand-alone drug plans did not cover⁵⁵. Orphan drugs are often in high cost-sharing tiers or require prior authorization⁵⁵. Due to the enormous expense of orphan drugs in the US, many American patients with stand-alone drug plans must pay large out-of-pocket expenses or forgo treatment. 40% of Americans with deductibles of 5% or more of their income and 25% of Americans with deductibles less than 5% of their income report delaying or avoiding needed medical care because of the financial burden of their deductible⁵⁶.

Potential problems for reimbursement in Canada

In Canada, the federal and provincial governments are responsible for different aspects of healthcare. Federally, Health Canada is responsible for assessing the efficacy, safety, and manufacturing quality of orphan drugs⁵⁷. The Patented Medicine Pricing Review Board operates at the federal level to regulate the price of orphan drugs in Canada⁵⁷. However, each province makes its own reimbursement decisions for orphan drugs⁵⁷. Similar to the EU, there is a patchwork of access to orphan drugs based on different pricing and reimbursement policies in Canada. Currently, there are no provisions in the Canadian Framework to address unequal reimbursement practices between provinces¹.

Some have argued¹⁹ that reimbursement choices in Canada should be rooted in the ‘rule of rescue’ such that, in the absence of alternatives, patients with life-threatening diseases should receive treatment regardless of the cost. Others have argued it is appropriate to invoke the rule of rescue at the level of the individual. However, it should not be operationalized to allow whole groups to be exempted from the rules of opportunity cost at the expense of others in the population⁵⁸. Unfortunately, the rule of rescue does not provide for the realities of fiscal limitations facing Canadian provinces. The number of orphan drugs on the market is increasing steadily⁵⁴, and may become a significant threat to the sustainability of Canadian health care systems. Some have suggested that incentives for orphan¹² and for more general drug development⁵⁹ should be aligned with reimbursement criteria. Thus, Herder¹² advocates for the integration of social value and ethical considerations in the regulatory decisions leading to orphan drug designation. In addition to decreasing the potential for refusal of orphan drug coverage at the reimbursement stage, such mechanisms may optimize the efficiency of orphan drug development, and increase the likelihood of reimbursement by decreasing R&D costs¹². Exploring alternative reimbursement strategies and optimizing the efficiency of therapeutic development pathways would have far reaching consequences on the Canadian health care system beyond orphan drugs.

Conclusion

The draft Canadian Framework is similar to the implemented frameworks of the US, EU, and Japan, but lacks some essential safeguards against system misuse that may aid in increasing equity, justice and the economic sustainability of the program. Canada will likely face similar challenges to other jurisdictions in the implementation of its orphan drug framework and should capitalize on learning from their experiences.

A fundamental and pressing concern is that population prevalence definitions of rare disease are ambiguous and rapidly losing meaning, Canada should consider identifying target diseases for orphan drug designation based on unmet patient need, among other factors. Further, Canada is a relatively small market, and this should be factored into

local policy development. As such, Canada may be best served by allowing companies to earn relatively greater profits on orphan drugs compared with other jurisdictions to encourage market entry. Likewise, judicious provision of intellectual property protections to encourage R&D of innovator orphan drugs and ultimately of biosimilars, may maximize patient access and reduce payer costs. Canada should consider moving to coordinate the targeting of incentives to those orphan drugs most likely to be reimbursed by payers. Finally, the current framework lacks a plan to support equitable reimbursement of orphan drugs, thus patients in some provinces may not be able to access orphan drugs even if they have been approved for the Canadian market. We hope that this document will contribute to policy-makers further exploring and explicitly addressing the issues highlighted herein. Doing so should assist in the success of Canada's orphan drug strategy – ensuring access to treatments that will improve the lives of Canadians affected by orphan diseases.

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Appendix 1

Analytical Approach

We searched forward citations⁶⁰ to an article on orphan drug frameworks by McCabe et al.⁶¹ From identified forward citations, we generated targeted search terms for key issues, including: “orphan drug”, “legislation”, “regulation*”, “market exclusivity”, “patent*”, “incentive*”, “biologic*”, and “approval.” Using these search terms, we conducted targeted searches between April 25 and May 30, 2014 in PubMed, Scopus, and Google Scholar. We included 279 relevant references in our analysis. Included documents were in English and discussed orphan drug regulations or related regulations on incentives (e.g., on intellectual property) in the jurisdictions of interest (the EU, US, Japan, or Canada).

We used NVivo 10TM⁶² to analyse positive and negative comments on the implementation and operation of orphan drug frameworks. We identified repeated and related concepts in the analysed articles to develop initial codes for the comments⁶³. We iteratively compared the coding of new articles to old articles to identify similarities and differences that further informed the development of the codes⁶⁴. Finally, we organized the codes into broader categories (Points to Consider) that formed our analysis above.

We also searched the grey literature on orphan drug regulations and regulatory responses to issues with orphan drug legislation. We consulted orpha.net, an international reference portal for information on rare diseases, and publicly available government documents from the US and EU including the orphan drug legislation, reports on the impact of orphan drug legislation, and guidelines from regulators for orphan drug companies. Finally, we reviewed the initial draft discussion document for a Canadian Orphan Drug Framework to compare it to existing orphan drug legislation. We identified 81 documents, which we used as background, but did not include in our formal qualitative analysis.

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