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Regulatory, Reimbursement, and Pricing Barriers to Accessing Drugs for Rare Disorders in Canada

Pre-release Chapter

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Contents

Executive summary

The objective of this study is to provide an understanding of the impact of the drug regulatory review process, the reimbursement recommendation and price negotiation systems, and the procedure for controlling prices on Canadian patients' ability to obtain insurance-covered access to new drugs for rare disorders. The essay also considers the potential negative impact of changes proposed by the federal government to Canada's Patent Medicine Prices Review Board (PMPRB), whose primary role is to ensure that the maximum Canadian prices for patented medicines are not excessive.

The study first addresses what a rare disorder is and how rareness is assessed and defined in different jurisdictions. It outlines the time and effort required to bring treatments for rare disorders to the situation where they can be considered for human consumption, and presents some examples of new drugs for these disorders. It then examines the barriers that must be overcome in order to bring new medications for rare disorders to Canadian patients. These include the national regulatory review and approval process, the pricing controls presently in place in Canada, the health technology assessment processes that make recommendations regarding reimbursement to public drug insurance plans, the system established by federal, provincial, and territorial drug plans to negotiate prices with pharmaceutical manufacturers, the individual public drug plan negotiations, and the criteria that patients must satisfy before they can obtain insurance coverage. Finally, the study discusses the potential for the proposed revisions to the patented medicines regulations to be a much larger barrier to access to drugs for rare disorders than it is for more common disorders.

The proposed changes to the role of the PMPRB have created much uncertainty among patients and pharmaceutical manufacturers and have the potential to delay the launch of new innovative medications in Canada by decreasing the country's attractiveness to companies as a market for their products, especially for costly medicines, which include many drugs designed to treat rare disorders. The changes include altering the number and mix of countries that the PMPRB uses as the basis for setting the maximum allowable prices for patented medications in Canada by excluding two relatively high-priced countries—the United States and Switzerland—in favour of

countries with generally lower prices in order to decrease the prices of patented drugs. In addition, the federal government wants the PMPRB to perform assessments of the value of patented drugs based on cost-effectiveness analyses submitted to the Canadian Agency for Drugs and Technologies in Health, and to evaluate the anticipated market size of the drug over the first three to five years of use against Canada's per-capita gross domestic product as a proxy for an individual's buying power to assess the impact of the drug's proposed price on patient and insurer finances. If patented medications fail these tests, the PMPRB may require price reductions.

The complex processes required to bring new drugs for rare disorders to Canadian patients are already causing delays in patient access to these drugs, which extends patient suffering by failing to alleviate their unmet needs in as timely manner as possible. The creation of more barriers that will deter or delay pharmaceutical manufacturers from bringing the many new costly drugs for rare disorders in development to Canada denies both hope and health benefits to Canadian patients. Instead of making access to new costly drugs easier, it seems that federal government officials are presently fixated on a mantra of "affordability, accessibility and appropriate use of prescription drugs." The proposed sweeping changes to the PMPRB are part of this trend. Rather than providing hope to patients needing costly new drugs for previously untreatable conditions, Canadian governments appear to be moving towards a basic "pharmacare" system built on a formulary of inexpensive genericized drugs and a small, restricted-access list of specialty drugs, including drugs for rare disorders, limited to those available from manufacturers willing to negotiate substantial price reductions. Canadian governments and their associated organizations should be developing inventive and coherent nationwide policies to balance timely and fair access to all drugs, but especially those for rare disorders, with appropriately competitive pricing negotiations so that drugs are accessible to Canadians who need them.

Introduction

The objective of this essay is to provide an understanding of the impact of the Canadian regulatory, reimbursement recommendation, and price negotiation processes on access to new drugs for rare disorders in Canada. We first address what a rare disorder is and the time and effort required to bring treatments for some rare disorders to the point where they can be considered for human consumption. The potential for the national regulatory review and approval process to be a barrier to bringing a new rare disorder drug to the Canadian market is then examined. Finally, the delays in access caused by the Canadian reimbursement recommendation and price negotiation processes are evaluated. It is argued that the combination of these processes is causing delays in access to drugs for rare disorders and, consequently, extending patient suffering by failing to alleviate their unmet needs in as timely manner as possible.

For most of humankind's history, little could be done for most diseases, but this situation rapidly changed during the twentieth century (Rawson, 2016a). Today, many commonly occurring illnesses can be cured, alleviated, or prevented, and life expectancy and quality have increased dramatically. Much of this improvement, although not all, has been due to the development of drugs and vaccines.

Individuals diagnosed with rare disorders have not fared so well because until recent years few therapies have been available for them. Nearly seven thousand rare disorders have been identified, many of which are genetic in origin and begin to affect sufferers in early childhood (Dunoyer, 2011; Schieppati et al., 2008). Considerable diversity exists in their cause and their impact on the body. Most are severely physically and mentally disabling with serious consequences on the sufferer's quality and duration of life.

Examples of rare disorders are lysosomal storage diseases, which include Fabry, Gaucher, and Pompe diseases and the mucopolysaccharidoses. Other examples that readers may be familiar with are cystic fibrosis and phenylketonuria, while rarer disorders include tyrosinemia type 1 and atypical hemolytic uremic syndrome. Awareness of rare disorders has been promoted by advocates such as Jonathan Pitre, who suffered constant excruciating pain during his short life of 17 years from epidermolysis bullosa, a genetic condition that causes the skin to be extremely fragile and to blister easily (Dangerfield, 2018).

Rare disorders are an important public health issue and complex for healthcare providers to manage since only about 5 percent are treatable (National Organization for Rare Disorders, 2016). They result in increased healthcare spending because care is commonly uncoordinated, with long delays in diagnosis, many misdiagnoses along the way, and patients being passed between many types of medical specialists (Angelis et al., 2015; Dharssi et al., 2017). Considerable productivity is lost by the heavy burden placed on caregivers.

Measurement of the occurrence of rare disorders

One of the challenges in understanding the impact of rare disorders is the availability of reliable information on their occurrence. Disease occurrence is assessed by two principal measures: incidence and prevalence. Incidence is the number of new cases of a disease that occur during a specified period (commonly a year) in a population at risk of developing the disease, while prevalence is the number of cases of a disease in a population as a proportion of the total population at a specific time. The incidence of a rare disorder is frequently unknown because it is difficult to measure. Consequently, the occurrence of a rare disorder is often reported using prevalence.

Although knowledge of disease prevalence is important, it can be difficult to measure accurately when a disorder is extremely rare and is frequently expressed as a range rather than a specific number. Moreover, prevalence can vary by age, gender, geographic region, time, and genetics. For instance, cystic fibrosis prevalence is higher in individuals under the age of 30 because the median age of survival in sufferers is just over 53, although the median age has been rising over the last 20 years due to improved survival. Cystic fibrosis prevalence also varies by genetic mutation; for example, more than 89 percent of Canadian patients have a F508del mutation, whereas only 3 percent have G551D mutation (Cystic Fibrosis Canada, 2017). Further problems with estimating the prevalence of a rare disorder in Canada are that, apart from cystic fibrosis, phenylketonuria, congenital hypothyroidism, and medium-chain acyl-CoA dehydrogenase deficiency, newborn screening for rare disorders is limited and inconsistent across the country (Therrell et al., 2015), and patients often experience years of multiple visits to specialists, emergency departments and diagnostic tests before receiving a definitive diagnosis (Critical Care Services Ontario, 2017). As a result, the prevalence of some rare disorders may be underestimated.

Diseases form a continuum from commonest to rarest and, therefore, it is not surprising that no universal agreement exists about the prevalence point at which disorders are considered rare (**table 1**). A global assessment of the prevalence used to define a rare disorder demonstrated that most lie between 40 and 50 per 100,000 (Richter et al., 2015).

Table 1: Definitions of a rare disorder used in some countries

Rare disorder definition	Canada	Europe	United States	Australia	Globally
Prevalence less than	5 per 10,000 persons	5 per 10,000 persons		1 per 50,000 persons	0.5 to 7.6 per 10,000 persons
Disorder that affects			200,000 people*		

Sources: European Medicines Agency, 2018; Food and Drug Administration, 2017; Australia, 2018; Richter et al., 2015.

* Approx. 6.2 per 100,000 persons.

The Canadian definition of a rare disorder means that a broad array of disorders is included, ranging from juvenile idiopathic arthritis with a reported prevalence of approximately 45 per 100,000 individuals, through phenylketonuria whose prevalence is 10 per 100,000, to atypical hemolytic uremic syndrome that affects 2 to 5 individuals per million. In terms of Canadians, this means that there are about 16,000 with juvenile idiopathic arthritis, 3,600 with phenylketonuria and 180 with atypical hemolytic uremic syndrome. Thus, "rare disease" is in itself a spectrum of disorders from uncommon to ultra-rare.

For the purposes of this essay, a rare disorder is defined as one with a prevalence between ≤10 and >1 per 100,000 persons, while an ultra-rare disorder is one with a prevalence of ≤1 per 100,000 persons. An example of a rare disorder is phenylketonuria, a genetic condition that results in decreased metabolism of the amino acid phenylalanine. If untreated from the first months of life, phenylalanine builds up in the blood and excess amounts cross the blood-brain barrier, which can lead to profound mental retardation, seizures, and behavioural problems (Cunningham et al., 2012). Traditional phenylketonuria treatment is a lifelong, severely restricted diet low in foods containing phenylalanine, together with special supplements, that should begin as soon as possible after birth. Maintaining treatment can be challenging, especially during teenage years when young people want to be and do the same as their peers.

An example of an ultra-rare disorder is atypical hemolytic uremic syndrome, which is a progressive, genetic, autoimmune disease that can occur at any age. It causes damage to the lining of blood vessels that activates clotting, which impacts the function of various vital organs but most often the kidneys. Patients with atypical hemolytic uremic syndrome have a poor prognosis with a mortality rate of up to 25 percent and progression to end-stage renal disease in 50 percent (Noris and Remuzzi, 2009). When the kidneys stop working, dialysis is required which, although necessary to sustain life, is associated with significant comorbidities and worsening prognosis. Kidney transplant is not a viable option because disease recurs in 60 percent of patients and transplant

failure occurs in more than 90 percent (Bresin et al., 2006). Quality of life is also poor because atypical hemolytic uremic syndrome patients suffer from fatigue, hypertension, and neurological impairment, which, together with the need to have regular dialysis, limit their opportunities for regular employment and many of the normal activities of life.

Treatments for rare disorders

Until recently, little could be done for most rare disorders, other than treating symptoms and providing palliative therapies to alleviate suffering. Beyond this, rare disorder patients have been marginalized and largely ignored (Wästfelt et al., 2006) because the focus for many years has been on the development of medications for disorders that affect large segments of the population. However, with the sequencing of the human genome, researchers and pharmaceutical companies have begun to develop drugs for rare and ultra-rare disorders and several have been brought to the market (Janoudi et al., 2016; Rawson, 2017a). Many more are in the pharmaceutical pipeline.

The cost of developing any new therapeutic innovation is high. In 2000, the development of a drug from the discovery stage to submission of an application for marketing approval was estimated to take, on average, about $800 million and 10 years (DiMasi et al., 2003). By late 2014, the estimate was reported to have increased to $2.6 billion (DiMasi et al., 2016). The time and resources required to develop new innovative drugs for rare and ultra-rare disorders are just as substantial.

An example of the time and effort required to develop a drug for a rare disorder is presented by Wästfelt et al. (2006). Tyrosinemia type 1 is an inherited, life-threatening disease caused by a deficiency of the last enzyme of the tyrosine degradation pathway and characterized by progressive liver disease. In children who do not die from liver failure, there is an increased risk for hepatocellular carcinoma and survival beyond adolescence is extremely rare. Tyrosinemia type 1 was recognized as a disease during the 1960s, but its primary cause was unknown until the 1970s. In the late 1980s, a pharmaceutical company discovered that herbicidal chemicals were potent inhibitors of tyrosine degradation and that rats exposed to the chemicals developed corneal lesions, a hallmark of elevated blood tyrosine levels in both rats and humans. It was soon realized that a chemical of this type might be an effective drug to treat tyrosinemia type 1. When a small group of children were given a drug (nitisinone; Orfadin) developed from the chemicals in the early 1990s, the response to treatment was dramatic. A long-term clinical study was initiated by academic clinicians to evaluate whether nitisinone could serve as an alternative to liver transplantation. Approximately 400 patients worldwide have now been

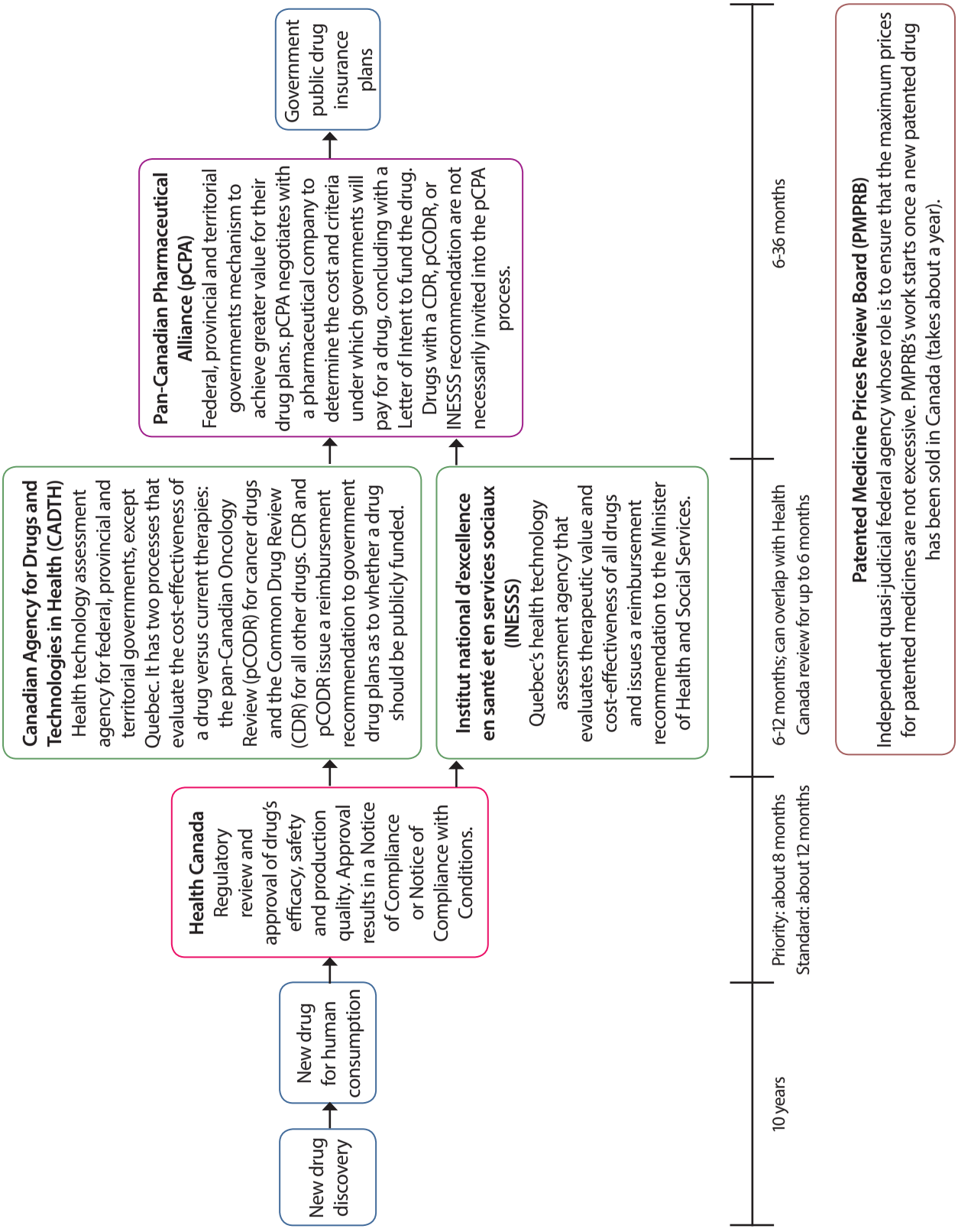
included in the study of which 320 have ongoing treatment. Nitisinone has improved the outcome of tyrosinemia type 1 (Lock, 2017), but more than 10 years elapsed before the drug was first approved in the United States and 14 years elapsed before its approval in Europe.

A large proportion of the new drugs for rare or ultra-rare disorders are indicated for lysosomal storage disorders, e.g. Fabry disease (Schiffmann, 2015), Gaucher disease (Mistry et al., 2015), Pompe disease (Chien et al., 2013), and the mucopolysaccharidoses (Muenzer, 2014), which are inherited metabolic diseases—characterized by an abnormal build-up of various toxic materials in the body as a result of enzyme deficiencies—that usually manifest in childhood (Parkinson-Lawrence et al., 2010). These disorders affect different parts of the body, including the skeleton, brain, heart, and central nervous system, and often lead to children dying at a young and unpredictable age after much suffering. Other drugs are indicated for a wide range of disorders, such as phenylketonuria, atypical hemolytic uremic syndrome, cystic fibrosis due to particular gene mutations, Dravet syndrome (a severe form of epilepsy with a high mortality rate), and cryopyrin-associated periodic syndrome (auto-inflammatory disease that may cause hearing and vision loss, mental impairment, significant bone deformities, and renal failure). Although they are not cures and frequently require continuous lifelong use, the new drugs for rare and ultra-rare disorders offer the potential to slow disease progression and change the course of disorders for the first time.

An example of a new drug for a rare disorder is sapropterin (Kuvan) for phenylketonuria. Phenylketonuria patients respond to sapropterin with differing degrees of successful reduction of brain-harming phenylalanine and, for some, neuro-cognitive improvement. Eculizumab (Soliris), which is an example of a new drug for an ultra-rare disorder, has been shown to improve kidney function, reduce blood vessel damage and decrease the risk of blood clots in atypical hemolytic uremic syndrome patients when used in a timely manner so that they are able to discontinue the traditional plasma therapy and dialysis and have a successful kidney transplant. In some cases, early use after a timely diagnosis has led to full recovery.

Bringing any drug to patients in Canada is a complex process with several barriers along the way that are often more difficult for manufacturers of drugs for rare and ultra-rare disorders to overcome than producers of medicines for more common disorders. **Figure 1** outlines the processes for regulatory approval and reimbursement recommendation in public drug plans in Canada.

Figure 1: Canadian regulatory and public reimbursement review processes and the time required



Barriers to getting new drugs to Canadian patients

Regulatory approval

The process of identifying a potential new drug and making it available to most Canadians can take many years (**figure 1**). The process is not only long but also tortuous.

The first step in bringing most new medications to Canadians is Health Canada's regulatory review, which assesses the efficacy, safety, and production quality of the new drug and takes about a year, although there is considerable variation in the time required to review and approve new drugs (Rawson, 2018a). For acceptable submissions, Health Canada issues a Notice of Compliance, which allows the marketing of the drug. In some cases, a Notice of Compliance with Conditions is issued, which requires the manufacturer to undertake additional studies of the new drug before a full Notice of Compliance can be issued; the review period is shorter for these drugs if advanced consideration for eligibility for a Notice of Compliance with Conditions is requested by the company before filing the submission.

In several countries, the pharmaceutical industry's focus on drugs for rare disorders has been stimulated by orphan drug policies designed to accelerate the development of first-in-class treatments and allow earlier access to patients. Manufacturers of drugs that achieve orphan status in Europe receive incentives such as market exclusivity for 10 years and fee reductions, while incentives in the United States for the development of orphan drugs are market exclusivity for seven years, waiver of submissions fees, and tax credits for clinical testing (Dharssi et al., 2017). These incentives have led to significant benefits for patients in the United States. Overall, the 209 orphan drugs approved in the United States between 1983 and 2014 were "highly innovative and provided substantial gains in reducing unmet needs for rare diseases" with over 50 percent of the drugs being first in their class and 78 percent receiving a priority review (indicating their importance); 35 percent of the drugs were approved for the treatment of rare cancers (Miller and Lanthier, 2016).

Health Canada proposed an Orphan Drug Regulatory Framework in 2012, but it was not enacted and, in October 2017, the current federal government deleted all references to the framework from the ministry's website without notice or consultation (Forrest, 2017). The Canadian Organization for Rare Disorders (2015) also proposed a rare disease strategy with the five goals of improving early detection and prevention, providing timely, equitable and evidence-informed care, enhancing community support, providing sustainable access to promising therapies, and promoting innovative research. This strategy has not been implemented by any level of government.

The impact of the lack of an orphan drug policy can be seen in the time taken to bring nitisinone to Canada. Nitisinone was developed, marketed, and distributed by a small biotechnology enterprise founded in Sweden in 1988 as a direct result of the financial incentives provided by the orphan drug legislation in the United States (Wästfelt et al., 2006) and was approved by the United States Food and Drug Administration in 2002. The drug also received orphan drug status in the European Union and was approved in 2004. It was not until 2016 before nitisinone was submitted to Health Canada and approved in the same year—more than 10 years after approval in Europe and the United States, and over a quarter of a century after the first patient received the drug.

Pharmaceutical manufacturers place Canada lower than the United States and Europe on their product launch sequence of countries. The submissions to Health Canada for 84 percent of the drugs for rare or ultra-rare disorders approved between 2002 and 2016 were filed after those to the Food and Drug Administration and the European Medicines Agency, with a median delay of 253 days (inter-quartile range: 102–670 days).[1] The median delay was shorter (208 days; inter-quartile range: 90–406 days) for the 30 companies with the largest annual dollar sales values than the median delay of companies with lower sales values (720 days; inter-quartile range: 164–1,385 days), which produced proportionally more drugs for rare and ultra-rare disorders. Some drugs do not come to Canada at all: 23 drugs for rare or ultra-rare drugs approved by the European Medicines Agency and/or the Food and Drug Administration between 2002 and 2016 were not approved in Canada by the end of 2016 (Rawson, 2018a). A planned increase of more than 70 percent in the regulatory review fee for new drugs (Canada, 2017a) may deter all companies from launching new drugs in Canada but may be a greater disincentive to smaller companies with innovative drugs for rare or ultra-rare disorders.

1. Half of the drugs have a delay shorter than the median and half have a longer delay. A quarter of the drugs have a delay shorter than the lower value of the inter-quartile range, while a quarter have a delay longer than the upper value.

Pricing controls

An enormous amount of literature has been produced concerning the negative consequences of price controls on the availability of drugs and drug research and development. Tighter pricing policies provide savings in the short term but come with social costs. These costs include significantly reduced new drug introductions (with those that are brought to the market being available later than in other jurisdictions), a negative impact on health outcomes and life expectancy, and a reduction in pharmaceutical company investment and employment (Moreno et al., 2016; Rawson, 2016b).

Since the late 1980s, the Patented Medicine Prices Review Board (PMPRB), which is an independent quasi-judicial body unique to Canada that works at arms-length from the federal Minister of Health (Canada, 2018), has had the primary role of ensuring that the maximum Canadian prices for patented medicines are not excessive. The PMPRB's work, which takes about a year to complete, starts once a new patented drug has been sold in Canada (**figure 1**). Since the first sale may be soon after regulatory approval or may only occur after a drug has public or private insurance coverage, the timing of the commencement of the PMPRB's actions is variable.

Presently, the PMPRB compares the price that a company is charging in Canada with prices in seven comparator countries (France, Germany, Italy, Sweden, Switzerland, the United Kingdom, and the United States) and sets a ceiling price based on uniqueness of the product and the Board's assessment of the drug's therapeutic benefit. This assessment can lead to a price reduction.

Because some believe it has been unsuccessful in controlling drug prices, the PMPRB is presently under review with the aim of reforming its processes (Canada, 2017b). The first of the proposed reforms is a change in the comparator countries which will remove the United States and Switzerland from the present seven countries and add Australia, Belgium, Japan, Netherlands, Norway, South Korea, and Spain. Since the new countries have tighter price controls, calculating the ceiling price based on the new 12 comparator countries is intended to lower prices in Canada.

Other changes are more radical and will be discussed in the section on **Proposed revisions to the Patented Medicine Prices Review Board**.

Health technology assessment for public reimbursement recommendation

Once a drug has received regulatory approval from Health Canada, the manufacturer faces the process of getting the drug insured by public and private plans. Most Canadians receive some degree of drug insurance coverage through federal, provincial, and territorial government-funded plans or

through private insurance paid for by individuals or cost-shared with employers, unions, or associations (Sutherland and Dinh, 2017). Government plans offer a degree of drug coverage to about 40 percent of the Canadian population but are mainly designed to provide insurance to seniors, social assistance recipients, and some special groups, such as children, cancer patients, or when costs are deemed to be catastrophic (Rovere and Skinner, 2015; Rawson, 2017b). Only the province of Quebec has a mandatory, mixed public-private, universal drug insurance plan.

To be considered for reimbursement in Canada's federal, provincial, and territorial public drug plans (with the exception of Quebec), pharmaceutical companies submit a health technology assessment application to the Canadian Agency for Drugs and Technologies in Health (CADTH) to demonstrate the value of the drug based on the clinical benefit of a drug in relation to its cost, i.e., its cost-effectiveness (**figure 1**).[2] In general, the health technology assessment process takes six to 12 months to complete.

CADTH often claims to be an independent organization, but it is important to recognize that it is owned, managed, and funded by federal, provincial, and territorial health ministries and, therefore, does not operate at arms-length from these governments (Rawson and Adams, 2017). Consequently, its reimbursement recommendation processes fail to adhere to the good governance principles of:

- **Accountability** to all stakeholders: CADTH is only truly accountable to its owners;
- **Transparency** for all concerned: some stakeholders have greater access to information than others;
- **Participation** by all stakeholders: patient participation is limited;
- **Equity**: all stakeholders should have opportunities to improve or maintain their wellbeing;
- **Responsiveness**: all institutions and processes should try to serve all stakeholders;
- **Consensus building**: good governance mediates differing interests to reach a broad consensus.

CADTH has two drug reimbursement recommendation processes: the pan-Canadian Oncology Drug Review (pCODR), which assesses cancer therapies, and the Common Drug Review (CDR), which evaluates all other drugs. At around 80 percent (Rawson, 2014), the pCODR positive reimbursement recommendation rate is significantly higher than the CDR rate of 50–55 percent (Griffiths et al., 2015; Rawson, 2015a; Rocchi et al., 2012).

2. The Institut national d'excellence en santé et en services sociaux evaluates drugs in Quebec in a manner similar to CADTH.

As a comparison, the positive reimbursement recommendation rate of the National Institute for Health and Care Excellence, which assesses all new oncology and most other new drugs for reimbursement in England's publicly-funded National Health System, is reported to be 76 percent (Griffiths et al., 2015).

Most positive recommendations from both pCODR and CDR are for drugs to be listed with clinical criteria and/or a need for a price reduction. Although CADTH does not publicly acknowledge having a cost-effectiveness ratio threshold for assessing drugs, evidence exists to suggest that $50,000 per quality-adjusted life-year is used, although not consistently applied (Rocchi et al., 2012). A higher threshold of around $150,000 appears to be used where there are unmet therapeutic needs or a lack of alternative options and when drugs for rare or ultra-rare disorders or cancer are evaluated. Negative recommendations are frequently based on the expert committee's opinion that a drug's efficacy evidence is inadequate (Rawson, 2017a; Rocchi et al., 2012) despite having been assessed by Health Canada's regulatory review as having acceptable efficacy.

The overall CDR positive recommendation rate obscures significant variation between different drug types. In particular, the rate for drugs for rare disorders has been much lower, especially for drugs for ultra-rare disorders. Drugs for rare disorders reviewed by the CDR between 2004 and 2015 had a positive recommendation rate of 56.5 percent, whereas the rate for drugs for ultra-rare disorders was only 23.1 percent (Rawson, 2017a). From 2016, the CDR positive recommendation rate for these drugs has improved substantially (**table 2**) for reasons that are discussed in the following subsection on **Price Negotiations for Coverage in Canadian Public Drug Plans**.

Recently, Richter et al. (2018) analyzed CDR recommendations for drugs for rare disorders and suggested that it may be inappropriate for CADTH to apply the same appraisal standard to drugs for ultra-rare disorders. However, the federal, provincial, and territorial government public drug plans do not appear to be in favour of this approach.

Table 2: Positive reimbursement recommendation rate in Common Drug Review reports of drugs for rare or ultra-rare disorders

Year of recommendation	Drugs for rare disorders (prevalence ≤10 to >1 per 100,000)	Drugs for ultra-rare disorders (prevalence ≤1 per 100,000)
2004 – 2015	13 (56.5%)	3 (23.1%)
2016 – February 2018	7 (87.5%)	7 (100.0%)

Source: Author's calculations based on Common Drug Review and pan-Canadian Pharmaceutical Alliance data.

Following the conclusion of a CADTH review, the next step for pharmaceutical manufacturers seeking public reimbursement coverage for their drugs is to seek admittance to the negotiating process established by the federal, provincial, and territorial governments. For private insurance reimbursement, pharmaceutical manufacturers negotiate directly with insurance companies.

Private drug insurance and health technology assessment

A large proportion of Canadians have access to private drug insurance through their employer, union, or associations. Private plans tend to offer much wider coverage, including brand name products, than the public plans, and the time taken to insure drugs is usually shorter. For example, of 464 new drugs approved for marketing by Health Canada between 2004 and 2013, 413 (89 percent) were insured by at least one private drug plan by January 31, 2015, compared with only 231 (50 percent) covered by at least one public plan (Rovere and Skinner, 2015, 2016). Furthermore, comparing only the drugs that have been covered by at least one public drug plan and at least one private drug plan, the average number of days taken to insure the new drugs was 132 days for private drug plans compared with 468 days for public drug plans.

Decisions about which drugs are covered depend on what employers, unions, and associations are willing to pay for, especially when new expensive drugs are considered. Insurance companies take note of recommendations made by Canada's health technology assessment agencies, but only one bases its coverage on their recommendations. Information about how decisions are made and which drugs are reimbursed by private insurance is not made publicly available. Price negotiations between insurance companies and pharmaceutical manufacturers are also confidential, but it is believed that private insurers pay higher prices than public plans.

Price negotiations for coverage in Canadian public drug plans

In August 2010, provincial and territorial governments, with the exception of Quebec, established a process known as the pan-Canadian Pharmaceutical Alliance (pCPA) to collectively negotiate prices of new drugs with pharmaceutical companies for public drug plans (Canada's Premiers, 2018). The process took several years to develop and the pCPA only became a formal entity with a permanent government-funded staff and office in 2015. In 2016, Quebec and the federal government joined the pCPA.

Drugs with a positive reimbursement recommendation are not necessarily invited into the pCPA process. The pCPA decides whether to open a

negotiation, which will determine both the cost and criteria under which governments will pay for a drug, concluding with a Letter of Intent to fund the drug. As of April 30, 2018, the pCPA reported that 208 negotiations (69.1 percent) have been successfully completed and 22 (7.3 percent) closed because agreement could not be reached (Canada's Premiers, 2018). In addition, the pCPA decided not to negotiate either collectively or individually at the drug plan level for 58 products (19.3 percent), while it deferred 13 negotiations (4.3 percent) to direct interaction between the manufacturer and individual drug plans.

The pCPA is designed to capitalize on the combined governments' buying power, with the objectives of increasing access to drug options, achieving lower drug costs and consistent pricing, and improving consistency of coverage criteria across Canada. The cost-containment objective seems paramount. The pCPA, like CADTH, is owned, funded, and governed by the federal, provincial, and territorial governments. Although it is understandable that manufacturers and governments want to keep the details of price negotiations confidential, the pCPA's policies, processes and practices are not publicly transparent (Husereau et al., 2014; Rawson, 2016c). Consequently, an evaluation of the pCPA's effectiveness based on publicly available information is not possible.

Since May 2016, pCPA representatives are included in CADTH processes to provide an opportunity for the pCPA "to receive relevant information on drugs reviewed through the CDR and pCODR processes" (CADTH, 2016). The pCPA is an observer at meetings of CADTH's expert committees and their advisory groups and receives confidential information from the recommendation processes. CADTH representatives attend pCPA meetings. Thus, CADTH and the pCPA are now closely interconnected.

An objective of the CADTH-pCPA integration appears to be to ensure that a negative reimbursement recommendation from CADTH results in no pCPA negotiation and a positive one sets up negotiating factors between the pCPA and manufacturer, usually the need for a substantial price reduction (Rawson, 2017a). This is one of the reasons for the increase in positive CDR recommendations (**table 2**) and for 11 (85 percent) of the 13 CDR reports for drugs for rare or ultra-rare disorders with a positive recommendation posted between January 2016 and February 2018 including comments that substantial price reductions of 42 to 97 percent would be required to approach an acceptable level of cost-effectiveness.

Public drug plan access

A drug that is successfully negotiated through the pCPA is reviewed yet again by each federal, provincial, and territorial government for its potential budget impact on their drug plan. A pCPA Letter of Intent does not guarantee that

all plans will provide coverage for the drug. Manufacturers must negotiate on the basis of the Letter of Intent with each public drug plan. Each drug plan is free to negotiate further discounts or other conditions with the manufacturer beyond those in the Letter of Intent before including the drug in their formulary or other systems, or to refuse to insure it. Price negotiations with the pCPA and individual drug plans can take anywhere between six months and three years.

Insurance is designed to protect people from disastrous financial loss. In most schemes, a few policy holders receive major financial compensation and a small number receive some benefit, while the majority receive no benefit other than knowing they were protected from catastrophic loss; car insurance works on this basis. Consider applying this approach to prescription drug insurance using an example presented by Zitner (2015). If we assume that all the 180 Canadians with atypical hemolytic uremic syndrome receive eculizumab, which is estimated to cost $700,000 per year, the total cost would be $126 million. If each of the 36 million Canadians contributed $3.50 for health insurance, the drug costs of all the patients who could benefit from eculizumab would be covered. Now consider one of the most commonly prescribed drugs in Canada, levothyroxine, which is mainly used for hypothyroidism (thyroid hormone deficiency) and costs about $1 per pill. The Thyroid Foundation of Canada (2018) reports that hypothyroidism affects about 2 percent of the population, which means 720,000 Canadians have the condition. Assuming all 720,000 Canadians with hypothyroidism receive levothyroxine, the total cost is approximately $263 million and, if each of the 36 million Canadians paid premiums to buy levothyroxine for all the patients who need it, they would have to contribute $7.30 each. This means that the insurance cost per Canadian for levothyroxine is more than double the cost of eculizumab.

However, this perspective is not taken by politicians and bureaucrats working in a system designed to satisfy most of the population, where they are encouraged to make choices aimed at satisfying the majority of voters. Consequently, drugs like levothyroxine receive insurance coverage. On the other hand, because the cost per patient of drugs for rare and ultra-rare disorders is frequently high, these drugs are often not successfully negotiated through the pCPA and fail to receive public drug plan coverage, whether or not the overall impact on provincial budgets is comparatively low due to there being relatively few patients.

Table 3 shows the pCPA pricing negotiating status for 18 drugs for rare or ultra-rare disorders approved by Health Canada and reviewed by the CDR between 2011 and 2016. While just over half of the drugs that received a positive CDR reimbursement recommendation had a completed pCPA negotiation (at least six provincial drug plans provide some coverage for four of these drugs), none of the drugs that received a negative CDR recommendation had

Table 3: Common Drug Review reimbursement recommendation by pan-Canadian Pharmaceutical Alliance negotiation status for 18 drugs for rare or ultra-rare disorders reviewed between 2011 and 2016

		pan-Canadian Pharmaceutical Alliance negotiation status		
Common Drug Review recommendation	**Number**	**Completed**	**No agreement**	**None**
Positive	11	6 (54.5%)	5 (45.5%)	0 (0.0%)
Negative	7	0 (0.0%)	1 (14.3%)	6 (85.7%)

Source: Author's calculations based on Common Drug Review and pan-Canadian Pharmaceutical Alliance data.

a completed negotiation. Thus, a positive CDR reimbursement recommendation does not necessarily lead to a successful pCPA pricing negotiation and a completed pCPA negotiation does not result in automatic or timely listings in all provincial drug plans. A negative CDR recommendation, on the other hand, seems to almost guarantee that the pCPA will decide not to negotiate on pricing with the drug's manufacturer so that the probability that the drug will be listed in any provincial drug plan is low.

Moreover, even if a rare disorder drug does receive coverage, the provincial criteria may not be consistent with the CDR recommendation report criteria, so that access restrictions can result in few Canadian patients being able to receive reimbursement. As an example, sapropterin for phenylketonuria has been listed in the Government of Ontario's Exceptional Access Program since 2013, but patients who are suitable candidates are required to qualify for a six-month manufacturer-funded trial of the drug after which provincial coverage may be accessible for patients with a demonstrated positive response to the trial subject to complex and stringent criteria that have been criticized by Ontario phenylketonuria physicians as lacking clinical sense (Rawson, 2017b). Only two patients out of a potential 200 have qualified for provincial reimbursement.[3] As a further example, the Exceptional Access Program eligibility criteria for reimbursement for eculizumab for atypical hemolytic uremic syndrome are extensive, complex, and also do not seem to be based on scientific evidence; they lead to the drug usually being reserved for acute patients and those who have had a kidney transplant, but not all patients have access.

In addition, the provincial drug plans have complex systems of deductibles, copayments, and premiums (Rawson, 2016a) and, for many drugs, special or restricted access criteria or therapeutic substitution that results

3. Personal communication from John Adams, CEO, Canadian PKU and Allied Disorders Inc.

in variation in patient eligibility, out-of-pocket expenses, and coverage (Campbell et al., 2017; Demers et al., 2008; LeLorier et al., 2008), which can effectively impede patient access. Access restrictions based on cost-containment reasons can also increase the potential for a negative effect on patient health. For example, Sheehy et al. (2008) found that the impact of Quebec's restrictive access to clopidogrel, an anti-platelet agent that reduces the risk of thrombosis (a complication often resulting in death) following coronary intervention with stenting was associated with 20 percent of patients either not receiving the drug or receiving it after a delay, which increased the risk of all-cause mortality. Similarly, in Ontario, the removal of a prior authorization requirement led to an increase in the rate of use of clopidogrel within 30 days after discharge from hospital after a heart attack from 35 percent to 88 percent, and the rate of admission for a further attack, a repeat percutaneous transluminal coronary angioplasty, or coronary-artery bypass grafting or death within one year after discharge decreased from 15 percent to 11 percent (Jackevicius et al., 2008).

Several drugs for rare or ultra-rare disorders that have received government drug plan coverage have only done so as a result of patient support group advocacy (Rawson, 2015b). By the nature of each disease, only a relatively small number of patients suffer from them and, as such, have limited resources to undertake the kind of persuasive, resilient, and tenacious advocacy action plan that is necessary to motivate politicians and bureaucrats to reimburse new, costly therapies in public programs. Although it is not always in their best interest (Chidi et al., 2016), governments in Canada would rather spread money thinly to large numbers of people, even if they do not need it—as is the case with the new Ontario drug plan for children and young adults (Rawson, 2017b)—because the patients and their families and friends represent a greater number of potential voters. Providing large funds for a small number of rare disorder patients is not so politically attractive. Federal, provincial, and territorial governments are either ignoring or out of touch with the reality of the increasing trend in pharmaceutical development towards "designer" drugs that target specific types of patients.

Proposed revisions to the Patented Medicine Prices Review Board

In addition to the proposed change in the PMPRB's comparator countries discussed earlier, the work of the PMPRB will include new review processes.

New patented drugs will be classified as high, medium, or low priority based on their anticipated impact on Canadian patients and public and private drug plans. A drug that is first in class, has few or no therapeutic alternatives, provides significant therapeutic improvement over existing treatment options, is indicated for a condition that has a high prevalence in Canada, has a high cost per patient, or is considered by Health Canada or other agencies to be important due to an unmet medical need will be classified as high priority. High priority drugs will be subject to a PMPRB review to determine whether their price is potentially excessive. Drugs for rare and ultra-rare disorders are highly likely to fall into this category because they are frequently costly and often for disorders with no effective therapeutic option.

The review will begin with a comparison of the proposed Canadian price with those in the 12 comparator countries. If a drug passes the country-comparator test, it will be subjected to a new cost-effectiveness test in which the PMPRB will assess the value of the drug based on the cost-effectiveness analysis submitted to CADTH and apply a $60,000 to $150,000 cost-effectiveness threshold to CADTH's assessment such that if CADTH's incremental cost-effectiveness ratio estimate is above it, the drug will not be insured. If a drug meets the cost-effectiveness threshold, the PMPRB will consider the anticipated market size of the drug over the first three to five years of use against Canada's per-capita gross domestic product as a proxy for an individual's buying power to evaluate the impact of the drug's proposed price on patient and insurer finances. Should the potential impact be considered to be too high, the price may be further adjusted. For drugs that fail these tests, the manufacturer will have an opportunity to explain why the price is not excessive and to provide confidential commercial information in support of their position, including any proposed non-transparent rebates and discounts to direct and indirect payers in Canada.

The proposed changes in the PMPRB's practices has created much uncertainty among patients and pharmaceutical manufacturers, which has the potential to delay the launch of new innovative drugs in Canada by decreasing its attractiveness to companies as a market for their products, especially expensive drugs (Rawson, 2018b). The proposed changes are anticipated to result in reductions in the price of drugs for rare and ultra-rare disorders by 70 to 90 percent, which would be a major disincentive to the marketing of these drugs in Canada because not only will the maximum allowable prices not cover the costs of distributing the drugs, but selling at such low prices would lead to demands for lower prices in other countries that use Canada as a comparator. A large body of evidence has demonstrated that pharmaceutical manufacturers rationally prefer to delay marketing a new drug or not to market it in countries with tight pricing controls (Danzon et al., 2005; Kyle, 2007). Consequently, although it is difficult to anticipate the impact of the proposed PMPRB revisions due, in part, to the lack of detail presently available, the information so far available has raised significant concern among individuals with rare disorders.

Conclusion

Several new drugs for rare and ultra-rare disorders have been launched in recent years. However, it is important to remember that 95 percent of rare disorders remain untreatable and cause much suffering and premature death (National Organization for Rare Disorders, 2016).

When drugs for rare and ultra-rare disorders are available, a significant number are approved in the United States and/or Europe but not in Canada. Even when drugs for rare and ultra-rare disorders receive regulatory approval in Canada, more than 95 percent do so after approval in the United States or Europe, with a median delay of 340 days (inter-quartile range: 183 to 949 days) (Rawson, 2018a). Nitisinone, for example, was approved by the Food and Drug Administration and the European Medicines Agency in January 2002 and November 2004, respectively, whereas Health Canada approved it in December 2016.

The regulatory review is only one barrier to getting new drugs to patients. Others include price control, CADTH health technology assessment for reimbursement recommendation, price negotiation between the pCPA and the manufacturer, and negotiations between the manufacturer and individual drug insurers. Access to new drugs, especially to rare or ultra-rare disorders, can be delayed or denied by any of these barriers. Even when they are listed by a public drug plan, drugs for rare and ultra-rare disorders are frequently only accessible to Canadians who satisfy criteria that are often restrictive and do not always make clinical sense. Thus, Canadian patients with rare disorders face numerous barriers to obtaining access to the drugs they need.

Instead of making access to new costly drugs easier, federal government officials are presently fixated on a mantra of "affordability, accessibility and appropriate use of prescription drugs" (Canada, 2017c). This appears to involve limiting insurance to low-cost drugs or drugs whose price can be regulated or negotiated down to a level that governments deem to be acceptable—a direction that will lead to access to new drugs being more restricted and healthcare providers being constrained to providing less than optimal care to their patients, which would not qualify as appropriate drug use. The proposed sweeping changes to the PMPRB are part of this trend. Rather than

providing hope to patients needing costly new drugs for previously untreatable conditions, Canadian governments appear to be moving towards a basic "pharmacare" system built on a formulary of inexpensive genericized drugs and a small, restricted-access list of specialty drugs (including drugs for rare and ultra-rare disorders) limited to those available from manufacturers willing to negotiate substantial price reductions.

Canadian governments and their associated organizations should be developing inventive and coherent nationwide policies to balance timely and fair access to all drugs but especially drugs for rare and ultra-rare disorders, with appropriately competitive pricing negotiations so that drugs are accessible to Canadians who need them. Affordability and accessibility should be implemented together, not as one or the other, and should lead to truly appropriate drug prescribing. The creation of more barriers to deter or delay pharmaceutical manufacturers from bringing to Canada the many new costly drugs for rare and ultra-rare disorders in development denies both hope and health benefits to Canadians with unmet health needs.

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