

Waiting for New Medicines

How Does Canada Compare to the
United States and Europe?

Nigel Rawson



Waiting for New Medicines

How Does Canada Compare to
the United States and Europe?

by Nigel S.B. Rawson

Contents

Executive Summary / i

Background / 1

Later Submission of New Drug Applications in Canada / 3

Population Size and Distribution / 5

Regulatory Process / 7

Intellectual Property Protection / 9

Health Technology Assessment / 10

Price Negotiation with Government Drug Plans / 13

Government Drug Plans / 14

Patented Medicine Prices Review Board / 15

Conclusion / 18

References / 20

About the Author / 28

Acknowledgments / 28

Publishing Information / 29

Purpose, Funding, and Independence / 30

Supporting the Fraser Institute / 30

About the Fraser Institute / 31

Editorial Advisory Board / 32

Executive Summary

The process of obtaining authorization to market a new medicine in Canada is similar to that in other industrialized countries. However, new medicines are approved in Canada later than in the United States and the European Union because drug developers submit applications later in Canada. For example, Barua, Westcott, and Vo (2021) found that the median difference between submission in Canada and the United States was 170 days, and between submission in Canada and the European Union was 123 days. The question is: why are medicines submitted later in Canada than in the United States and the European Union?

This study explores factors such as population size, geography, and the attractiveness of its pharmaceutical environment that lead to delayed submissions in Canada. Although it has a population similar to some European countries, Canada is an isolated, geographically huge market with a relatively small population and, therefore, a low population density.

Although population size and geography matter, they are only part of a manufacturer's decision-making when deciding where to launch new medicines. A favourable pharmaceutical environment is imperative. This includes incentives to encourage manufacturers to submit new medicines for regulatory review, strength of intellectual property rights, processes for health-technology assessment, price negotiation and price regulation, and policies and criteria put in place by insurance providers for coverage and patients' access to medicines.

Health technology assessment processes in Canada are a major impediment to getting new medicines to patients. Despite claims of independence, the Canadian Agency for Drugs and Technology in Health (CADTH) is owned, funded, and managed by the governments to whom CADTH reports, a clear conflict of duty. CADTH reimbursement recommendations frequently include overly restrictive clinical criteria that patients must satisfy to obtain insurance coverage. These criteria can be questionable and, in some cases, harmful.

Government drug plans also own, govern and fund the pan-Canadian Pharmaceutical Alliance (pCPA), which negotiates drug prices with manufacturers on behalf of all federal, provincial, and territorial drug plans. CADTH and the pCPA have been aligning their processes for several years. Although not its role, CADTH's reviews regularly include a recommendation for a price reduction to achieve cost effectiveness, which allows CADTH to set up an initial negotiating position for the pCPA if

it chooses to negotiate with the manufacturer. When there is no negotiation or an unsuccessful one, the chance of gaining coverage in government drug plans is low and, even when successful, coverage by the government drug plan is not guaranteed.

Added to these disincentives is the federal government's intention to regulate significantly reduced drug prices in Canada. This led to an extraordinary degree of uncertainty following the government stating its intention in 2015 to change the regulations of the Patented Medicine Prices Review Board (PMPRB), the government's quasi-judicial agency tasked with preventing time-limited drug patents from being abused. The proposed changes roused much opposition among drug developers and profound concern among patients. However, they have been scaled back with the principal remaining change being in the countries included in the PMPRB's international price comparison test.

Although the federal government has stayed further changes at this time, it has not relinquished its objective of reducing drug prices. Consequently, it seems highly likely that manufacturers will continue to wait and see before launching new medicines in Canada. If this is a common occurrence among manufacturers, submissions of new medicines in Canada will, at best, be delayed longer than they already are and, at worst, not happen, which will affect all Canadians.

Delays in medicines being submitted for marketing authorization in Canada place Canadians' access to innovative medicines at risk. It is essential for government policy towards new innovative medicines to change from its present focus on price control and other access-restricting actions to reviving biopharmaceutical innovation, research and manufacturing, and ensuring patient access. Further delays in access or complete denials of access to innovative medicines will hurt even more Canadians with unmet or poorly met health needs that could be helped by new medicines.

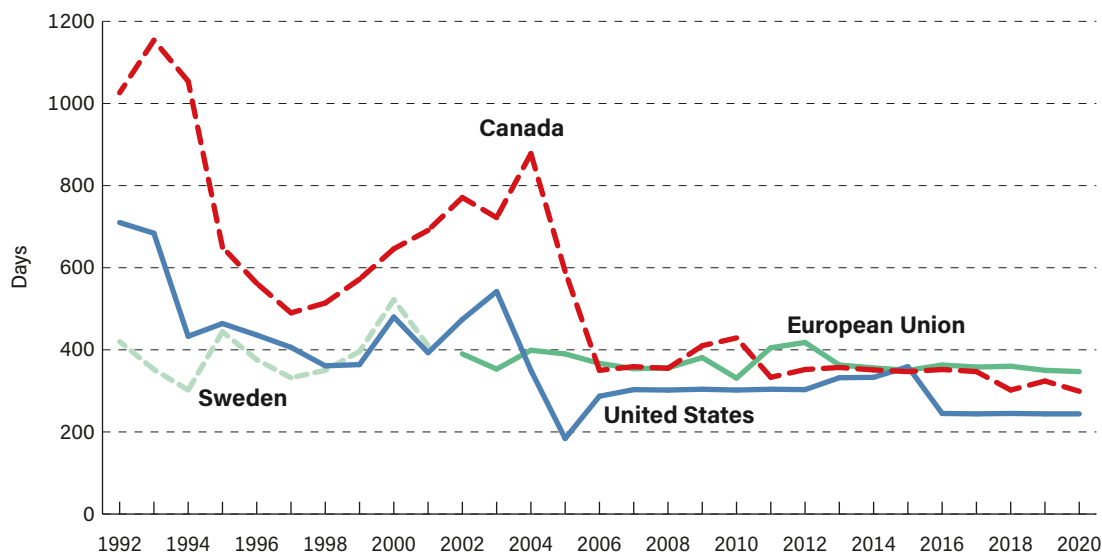
Background

In broad terms, the process of obtaining authorization to market a new medicine in Canada is similar to that in other industrialized countries (Paul, 2001; Rawson, 2003). After successful completion of laboratory and clinical trials in animals and humans, the manufacturer files a new drug submission with Health Canada that should provide the government department with sufficient information for the review and evaluation of a drug's suitability for marketing. The evidence submitted to Health Canada is usually the same as that submitted to the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Reviewers examine information in the submission to ensure that the product meets efficacy and safety standards, the manufacturing methods and controls are satisfactory, and the proposed labeling is adequate. If acceptable, Health Canada issues a Notice of Compliance, which authorizes marketing.

The timeliness of Health Canada's regulatory drug review and authorization process has been investigated since the mid-1980s. Much of the earlier work was performed by government-appointed committees (Eastman, 1985; Auditor General of Canada, 1987; Working Group on Drug Submission Review, 1987; Overstreet, Berger, and Turriff, 1989; Gagnon, 1992; Stroud, 1995) and had limited analyses. Nevertheless, almost all these investigations concluded that the Canadian drug-approval system was inefficient, resulting in prolonged review times. In the late 1990s, more detailed analyses began to be published comparing the time required to review and authorize new medicines by Health Canada with review times in the United States, some European countries, and Australia (Rawson, Kaitin, Thomas, and Perry, 1998; Rawson, 2000, 2003). These demonstrated that median times in Canada were around three years in the early 1990s and about two years during the decade between 1995 and 2005 but significantly shorter in the United States and Sweden (figure 1).

Representatives of Health Canada frequently suggested that longer review times were the result of a lack of human and financial resources (Cherney, 1998; Kondro, 2002; Peterson, 2002), despite an analysis demonstrating that the number of review staff did not appear to be a direct major determinant of the timeliness of Health Canada's performance (Rawson, 2002). An investigation of 14 drugs in Health Canada's system from 1995 to 1998 found that protracted review times were more likely the result of extensive downtime, when no one was working on the submission, between the

Figure 1: Median approval time (days) in Canada, the United States, Sweden, and the European Union, 1992–2020



Source: Rawson, Kaitin, Thomas, and Perry, 1998; Rawson, 2000, 2003, 2018a, 2023.

receipt of applications and initiation of the review and between components of the review (PricewaterhouseCoopers, 1999). The authors concluded that Health Canada reviews could be completed in a much shorter time if downtime was eliminated.

In the late 1990s, the introduction of a cost-recovery fee structure and performance standards for the review of new drug applications in Canada eventually led to the elimination of a backlog of applications, the reduction of downtime and, as a result, shorter review times starting in the mid-2000s (figure 1). The outcome has been that Health Canada's median review time has been a little under a year for most of the past 15 years, which is broadly consistent with FDA and EMA median times (Rawson, 2018a).

Later Submission of New Drug Applications in Canada

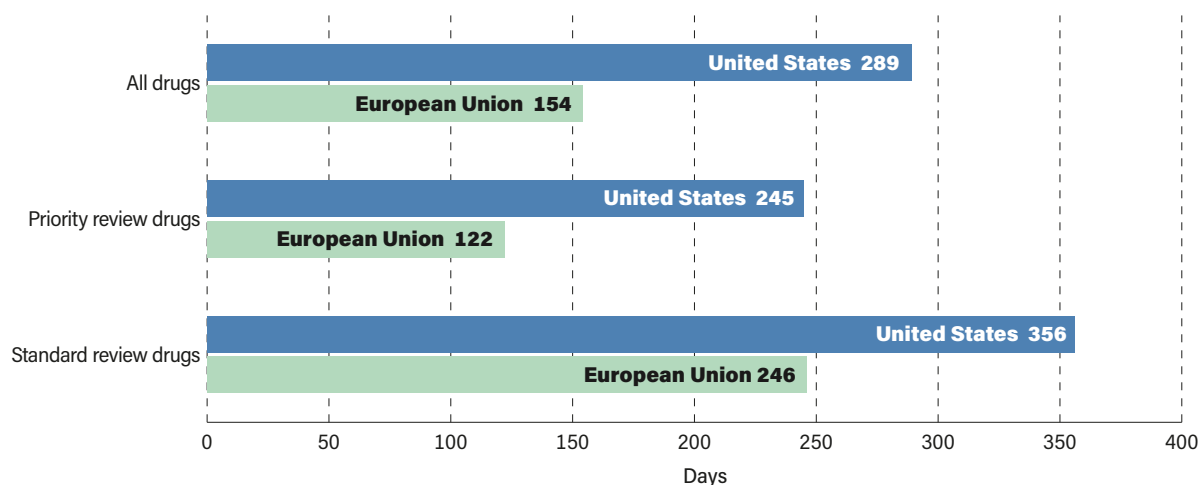
Nevertheless, new medicines are authorized in Canada later than in the United States and the European Union because drug developers submit applications later in Canada (Downing, Aminawung, Shah, Braunstein, Krumholz, and Ross, 2012; Shajarizadeh and Hollis, 2015; Rawson, 2018a; Barua, Westcott, and Vo, 2021). This results in Canadians having to wait for new medicines that can reduce suffering and extend lives and also decrease the need for other more expensive health care, such as admission to hospital. Delaying timely access to innovative medicines not only has a negative impact on individual patients but also a societal cost: greater use of the health-care system, increased caregiver requirements, and productivity losses as a result of inability to work (Conti, Frank, and Gruber, 2021). The benefits brought by new medicines can help to alleviate the burden on the already over-strained health-care system and produce significant cost reductions. Drugs may even lead to savings in pharmaceutical expenditure per life year saved before age 85 (Lichtenberg, 2019).

Barua, Westcott, and Vo (2021) demonstrated the extent of the delay between approval in the United States and the European Union compared with authorization in Canada. They analyzed 218 drugs approved in both Canada and the United States and 205 drugs approved in both Canada and the European Union between 2012/13 and 2018/19 and found that medicines were approved a median of 289 days earlier in the United States and a median of 154 days earlier in the European Union (figure 2). Corresponding figures for drugs receiving a priority or a standard review are also shown in figure 2.

Values of 289 and 154 days may not seem especially long. However, the median is the mid-point of the delays, so half the delays in approval are longer. The corresponding average delays observed by Barua, Westcott, and Vo for approvals in Canada compared to the United States (469 days) and the European Union (468 days) show that delays for some medicines extended for years.

Where available, Barua, Westcott, and Vo also examined differences in the dates of submission to the three regulatory organizations. The median difference between submission in Canada and the United States was 170 days and between submission in Canada and the European Union, 123 days, while the average differences were much larger at 468 and 404 days, respectively. The delay is substantial for some medicines.

Figure 2: Median number of days drugs were approved in the United States and the European Union before they were approved in Canada, 2012/13–2018/19



Source: Adapted with permission from Barua, Westcott, and Vo, 2021: fg 1.

Other data covering the period between 2002 and 2016 showed a median delay of 166 days (inter-quartile range: 67 to 491 days) between the first submission to either the FDA or the EMA and submission to Health Canada (Rawson, 2018a).

The question is: why are medicines submitted later in Canada than in the United States and the European Union?

Shajarizadeh and Hollis (2015) proposed four reasons for later submissions in Canada directly related to the review process: [1] the submission requirements could be more onerous than other agencies; [2] the value of getting early listing in Canada is small relative to potential harm to submissions elsewhere if Health Canada requires more information; [3] limited capacity in companies to make submissions leads to prioritization by potential market profitability; and [4] the desire of companies for regulatory approval in higher-priced markets first prompts them to delay submissions to Health Canada. Using medicines authorized by Health Canada, the FDA, or the EMA between 2000 and 2011, each reason was assessed, but none adequately explained submission delays. Shajarizadeh and Hollis did not, however, consider factors that affect the attractiveness of Canada's pharmaceutical environment to drug developers for marketing their products.

The attractiveness of the pharmaceutical ecosystem as a market for new medicines is extremely important and has multiple facets. These include its population size and distribution, aspects of the regulatory review, strength of intellectual property rights, processes for health technology assessment (HTA), price negotiation and price control, and policies and criteria put in place by insurance providers for patient coverage, and access to medicines.

Population Size and Distribution

Canadian government officials have compared Canada with European countries, stating that the size of Canada's population is similar to several European countries and that both the European Union and Canada have centralized regulatory authorities for the approval of medicines. They also note that several European countries have lower prices than those in Canada but often have new medicines introduced earlier than in Canada (Cooke, 2020). They conclude that forcing lower drug prices in Canada will not affect the timeliness of new drug submissions. It is not possible to say whether this is naïve thinking or political deceit.

These government officials overlook or deliberately ignore the facts that the European Union as a whole presents a market size of over 447 million (more than ten times that of Canada), that Europe is much more geographically compact than Canada (the median population density in the European Union is 108 persons per square kilometre with a range of 18 in Finland to 1,380 in Malta), that many European countries—both large and small—have pharmaceutical company headquarters or major research and manufacturing facilities within their borders, and that many European governments offer a collaborative approach to working with the biopharmaceutical industry.

In contrast, Canada is an isolated, geographically huge market with a relatively small population of 38 million and a population density of four persons per square kilometre. Although about half Canada's population lives in comparatively compact areas between Windsor and Quebec City and in British Columbia's lower mainland, the other half is widely scattered across a vast area. This poses unique challenges for marketing, selling, and distributing given the expense and time needed to educate health professionals spread across the country on new medicines and the costs of warehousing products and delivering them to widely dispersed health-care facilities.

Although population size matters to biopharmaceutical manufacturers—this is demonstrated by the precedence given to the United States and the European Union over Canada as a marketplace and the even lower significance accorded to Australia with a population of 25 million and New Zealand with a population of five million (Rawson, 2020a)—it is not the only factor in a manufacturer's decision-making around where to launch new medicines. A favourable pharmaceutical policy environment is imperative.

The attitude of Canadian federal governments towards the industry has been antagonistic for decades (Rawson and Adams, 2021a; Wells, 2021). Consequently, Canada needs to do even more to overcome its competitive disadvantage in geographical situation and population size. Improvements in the pharmaceutical environment are required to entice manufacturers to launch their medicines in Canada.

Regulatory Process

Regulatory reviews are similar in Canada, the United States, and the European Union in terms of the type of evidence reviewed (Paul, 2001). Nevertheless, differences exist in how important therapeutic advances are prioritized in their regulatory processes.

For instance, *Roctavian* is a new medicine for severe hemophilia A, a genetic bleeding disorder in which sufferers lack the normal ability of blood to clot after an injury due to a deficiency of an essential blood-clotting protein called Factor VIII. This deficiency places them at risk for painful, potentially life-threatening bleeds from even modest injuries. The standard of care is infusions of Factor VIII administered intravenously two to three times per week or 100 to 150 infusions per year. Sufferers' lives revolve around these infusions. Nevertheless, many continue to experience breakthrough bleeds, resulting in progressive and debilitating joint damage.

Few new hemophilia-A treatments have been introduced for decades. However, human genome sequencing has resulted in new gene therapies, like *Roctavian*, being developed for many previously untreatable or poorly treated disorders. For several years, *Roctavian* has undergone trials in humans that have demonstrated the drug's efficacy and safety. A single infusion of *Roctavian* results in lower levels of bleeding without need for infusions of Factor VIII.

The FDA has at least four programs that encourage drug developers to bring new therapies to patients who need them. The agency granted *Roctavian* orphan drug status, which is a program intended to advance the evaluation and development of products that demonstrate promise for diagnosis and/or treatment of rare disorders by providing tax credits for qualified clinical trials, exemption from regulatory fees, and seven years of market exclusivity after approval. The FDA also gave *Roctavian* priority review status, which means the FDA's review performance target is shorter than its usual standard. In addition, the FDA gave *Roctavian* breakthrough therapy designation—yet another program to allow Americans early access to important new medicines—and granted *Roctavian* regenerative medicine advanced therapy designation, which is a recently introduced program intended to facilitate the development and review of these new treatments for unmet medical needs in patients with serious conditions.

Like the FDA, the EMA has an orphan drug designation to encourage the development of these medicines. Manufacturers of orphan drugs receive study protocol assistance, 10 years of protection from market competition, reduced regulatory fees, and additional incentives for small to medium-sized developers. The EMA also has a scheme, known as Prime, designed to enhance support for the development of medicines targeting an unmet medical need; this includes early dialogue between the EMA and the developer and an accelerated assessment review. Medicines fulfilling an unmet medical need can receive conditional marketing authorization from the EMA if the benefit of its availability outweighs uncertainties arising from the need for additional data. Furthermore, the EMA has the ability to grant exceptional marketing authorization for medicines where the developer is unable to provide comprehensive data on the efficacy and safety under normal conditions of use because the condition to be treated is rare or because collection of full information is not possible or is unethical. The EMA reviewed *Roctavian* as an orphan medicine under its Prime scheme and gave the drug conditional marketing authorization in June 2022.

Health Canada has only two programs to encourage drug developers of innovative medicines: a priority review program and conditional marketing authorization. However, only a limited number of priority reviews can be coped with at a time and conditional marketing authorization is mainly reserved for oncology medicines. Health Canada is open to discussion with developers before submission is made but it has no programs similar to the EMA's Prime and exceptional marketing authorization scheme and no incentives for breakthrough medicines. The lack of incentives in Canada's regulatory review system makes it unsurprising that, so far, no submission for regulatory authorization for *Roctavian* has been made to Health Canada.

Health Canada claims to be a world-class regulator but it is not in the same class as the FDA and the EMA. The lack of incentives to launch new medicines in Canada and the limited opportunity for prioritization of a drug in the regulatory review process has a negative impact on Canada's attractiveness as a market for innovative medicines and likely deters developers of innovative medicines from submitting to Health Canada.

Intellectual Property Protection

Numerous deficiencies in the protection of intellectual property place Canada in the company of Mexico, Malaysia, China, and Russia in international comparisons (Lybecker, 2017). Two particular concerns to biopharmaceutical developers (Lybecker, 2017; Owens, 2017) with regard to Canada are:

- the period of patent restoration during which companies can recover time lost as a result of governmental regulatory authorization should be no less than the two-year minimum required by the Canada-EU Comprehensive Economic and Trade Agreement and preferably, be five years to be internationally competitive;
- protection for pharmaceutical data in Canada is only eight years, well short of Europe's 10 years (including market exclusivity) for small molecule drugs and far short of the advised period of 12 years for biologics data, which was adopted by the much more innovative United States.

In addition, Canada is one of only a few industrialized countries without an orphan drug policy to provide manufacturers with incentives to develop drugs for rare diseases. Orphan drug designation in the United States qualifies companies for tax credits for qualified clinical trials, exemption from user fees, and a possible seven years of market exclusivity after marketing approval, while the European Union orphan drug program offers reduced fees for regulatory activities, and ten years of market exclusivity after approval. None of these are available in Canada. An orphan drug program to encourage developers to bring these medicines to Canada is long overdue (Wong-Rieger, 2022).

Health Technology Assessment

To be considered for coverage by a government drug plan and some private insurance plans, a medicine must undergo a reimbursement review by Canada's two agencies providing a health technology assessment (HTA) for new drugs—Institut national d'excellence en santé et en services sociaux in Quebec and Canadian Agency for Drugs and Technology in Health (CADTH) for the rest of Canada—and receive a positive recommendation. HTAs are designed to provide an evaluation of a medicine's value as a guide to deciding whether a medicine should be funded by a health system.

CADTH's review process takes about a year. If manufacturers are able to take advantage of the opportunity to submit to CADTH before receiving marketing authorization from Health Canada, the time between marketing approval and CADTH's recommendation is reduced substantially.

To be fair to all stakeholders, HTA reports should not be compromised by significant conflicts of interest because this undermines the credibility of the reports (Goodman, 2020). Despite claims to the contrary (CADTH, 2022a), CADTH is not independent because the federal, provincial, and territorial governments to whom it reports own, fund, and manage CADTH. Consequently, CADTH fails the good governance principles of public accountability, transparency, fairness, and inclusivity of all stakeholders (Rawson and Adams, 2017). The continuing integration of CADTH's reimbursement recommendation processes with the provincial public drug plans' collective system for price negotiation with pharmaceutical companies (Rawson, 2022) reinforces CADTH's role as a non-independent partner in the pursuit of governments' cost-containment objectives, which should not be part of its function.

CADTH uses health economic analyses, as do other national HTA organizations, based on modelling techniques that require numerous assumptions and frequently use less than ideal, incomplete data. Although sophisticated methods have been developed in an attempt to overcome these issues, they can never truly overcome problems caused by unrealistic or illogical assumptions and inadequate data. As a consequence, results can vary widely, even between HTA agencies using the same data (Rawson, 2021). The analyses rely on a measure of disease burden known as a quality-adjusted life year (QALY) that attempts to include both quality and quantity of life lived but, in reality, is a deficient measure of an individual's quality of

health. [1] The results of the analyses are expressed as the cost effectiveness of the drug at a threshold of a specified number of dollars per QALY—commonly \$50,000 per QALY. However, this threshold, which first emerged 30 years ago (Grosse, 2008), was described 25 years ago as “arbitrary” and owing “more to being a round number than to a well-justified justification for a specific dollar value” (Garber and Phelps, 1997). Furthermore, the threshold has not been updated for inflation or increasing development costs. Many innovative medicines, especially those for rare disorders, exceed the \$50,000 cost-effectiveness threshold, indicating that it has not kept pace with modern scientific advances.

CADTH also tends to be slow in adopting new analytic methods. For example, a technique known as network meta-analysis, first proposed 25 years ago (Bucher, Guyatt, Griffith, and Walter, 1997), offers a method to interpret evidence from a set of trials for the same disease and outcomes but with multiple test drugs to derive indirect treatment comparisons to assess the relative clinical efficacy of the medications. Network meta-analysis has rapidly become a key method in HTAs for evaluating the relative efficacy of new medicines against existing drugs. Nevertheless, in an analysis of biologics to treat psoriasis given marketing approval in Canada, Australia, and the United Kingdom over the past 20 years, network meta-analyses were used in the submissions for all the biologics to HTA organizations in Australia, England, Wales, and Scotland but not by CADTH until 2016 (Rawson, 2021). This seemed to be the result of CADTH’s slow acceptance of this technique, with CADTH’s first guidance document on its use being published in October 2015 (Richter and Lee, 2015).

As another example, CADTH has also been slow in accepting the use of non-randomized clinical trials and real-world evidence in manufacturers’ submissions. For example, in 2015, the United Kingdom’s HTA agency stated in its review of *Soliris* for atypical hemolytic uremic syndrome (an extremely rare, life-threatening, chronic, progressive, genetic disease that can damage vital organs) based on non-randomized trials, an observational study and clinical expertise recommended funding as *Soliris* had a cost-effective benefit of “a magnitude rarely seen for any new drug” (NICE, 2015). In

[1] QALYs use a linear scale between zero and one, with zero and one being arbitrary values for death and full health, respectively. Thus, it is a one-dimensional measure of an individual’s quality of health. In reality, health quality is a complex, multi-faceted, and non-linear physical, psychological, and social state (Pettitt *et al.*, 2016; Prieto and Sacristán, 2003). QALYs fail to fully capture the social value of a medicine (Rowen, Azzabi Zouraq, Chevrou-Severac, and van Hout, 2017) and are an inadequate and inequitable measure of health quality for assessing the value of treatments for people with disabilities, chronic conditions, or rare disorders (National Council on Disability, 2019; Richter, Janoudi, Amegatse, and Nester-Parr, 2018).

contrast, CADTH concluded on the same evidence that the clinical benefit of *Soliris* could not be adequately established because the reviewers wanted randomized clinical trials, which are difficult to perform with ultra-rare disorders (CADTH, 2013). Only in 2022 has CADTH embarked on understanding real-world data and working towards accepting real-world evidence in HTA submissions.

It is crucial that CADTH accepts cutting-edge methods approved by other HTA agencies for two reasons. First, it allows drug developers to use the same analyses in their submissions. Requiring developers to perform different research for CADTH acts as a deterrent against launching their medicines in Canada. Second, acceptance of new methods of assessing the benefits of innovative medicines can lead to new drugs being made available to patients earlier (Tandon and Kakkis, 2021).

CADTH reimbursement reviews regularly include a recommendation for a price reduction, often a specific large percentage, to achieve cost-effectiveness at the \$50,000 threshold. However, CADTH's role is not to set prices, but comments (usually indicating the need for a price reduction) now appear as a regular component of its reimbursement reports.

CADTH reimbursement recommendations also usually include criteria that patients must satisfy to obtain insurance coverage. The extent of these criteria ranges from minimal to extensive and, for rare disorders, have been increasingly moving towards the latter (Rawson, 2022). The criteria can also be questionable, even harmful (Begovic, 2022). For instance, CADTH's most recent recommendation for *Trikafta*, a medicine that should provide benefit to most cystic fibrosis sufferers, includes a requirement for baseline respiratory measurements that necessitate patients cease earlier therapy, whose effectiveness has been waning in some patients, for two to three weeks and become sicker before having measurements taken to see whether they qualify for *Trikafta* (CADTH, 2022b). This is unnecessary suffering.

Highly restrictive patient-access criteria are a further disincentive for submitting new medicines for marketing approval in Canada. If the market potential is limited by HTA recommendations on prices or access criteria, drug developers are likely to prioritize launching new medicines in other less restrictive markets.

Price Negotiation with Government Drug Plans

Government drug plans also own, govern, and fund the pan-Canadian Pharmaceutical Alliance (pCPA), which negotiates drug prices with manufacturers on behalf of all federal, provincial, and territorial drug plans. CADTH and the pCPA have been aligning their processes for several years in the name of efficiency. This alignment seems designed more as budget management than health-care improvement (Rawson, 2022).

As noted in the previous section, CADTH reviews regularly include a recommendation for a price reduction. This allows CADTH to set up an initial negotiating position for the pCPA if it chooses to negotiate with the manufacturer. The alignment of CADTH's reimbursement recommendation processes with the provincial public drug plans' collective system for price negotiation with pharmaceutical companies reinforces CADTH's role as a non-independent partner in the pursuit of governments' cost-containment objectives, which should not be part of its function.

Manufacturers of new medicines reviewed by CADTH do not automatically enter a price negotiation with the pCPA. The pCPA is not required to try to negotiate; negotiation is by invitation. The pCPA rarely invites the developer of a medicine that received a negative HTA recommendation to negotiate and these drugs are rarely covered by government drug plans. Details of the outcome of a price negotiation, whether successful or not, are confidential for business reasons. As a result, patients have no knowledge of the process, which is especially concerning when a negotiation is unsuccessful and drug plans refuse to cover the medicine. The lack of transparency also means that the pCPA is only accountable to the governments that fund and manage the organization, not patients (Rawson, 2019a).

Negotiations with the pCPA should take less than six months (pCPA, 2022) but they frequently take longer. This adds yet another delay to impede drug developers' ability to maximize marketing.

Government Drug Plans

Unlike Australia, where there is one HTA agency and price negotiations are conducted with the federal government which, if successful, assures all states and territories provide the same coverage (Rawson, 2021), manufacturers in Canada have to surmount HTA and price negotiations and still have to successfully negotiate with individual government drug plans. Even if a medicine receives a positive reimbursement recommendation and has a successful price negotiation, coverage in government drug plans is not guaranteed.

Working with governments to negotiate coverage can take months to years, which delays sales. Drug plans have varied approaches to how they cover drugs and which drugs they cover, which adds an extra administrative burden that can also cause delays. Some drug plans cover new medicines more willingly and rapidly than others. For example, the Atlantic Canadian provinces and British Columbia have a lower coverage rate for rare disorder drugs than the other provinces (Rawson, 2020b; Ward, Chambers, Mechichi, Wong-Rieger, and Campbell, 2022) and Canadian provinces' coverage rates of these medicines are less than half the rates in several European countries and they take much longer to approve coverage (Ward, Chambers, Mechichi, Wong-Rieger, and Campbell, 2022).

Canadian government drug plans also frequently only cover new medicines subject to special access criteria that, while modeled on CADTH criteria, can be even more restrictive (Rawson, 2022). These criteria limit both manufacturers' ability to sell their medicine and its availability to patients.

Patented Medicine Prices Review Board

When first elected in 2015, Canada's current federal government promised to negotiate reduced prices for prescription medicines for government drug plans. Canada has subsequently experienced an extraordinary degree of uncertainty about federal intentions regarding the regulation of drug prices, especially following the announcement of proposed changes to the regulations of the Patented Medicine Prices Review Board (PMPRB), the government's quasi-judicial agency tasked to prevent time-limited drug patents from being abused. It is worth noting that, since the PMPRB's establishment in 1987, little abuse has occurred.

The PMPRB has performed its role over the past 35 years using a reference pricing test in which a company's intended list price for a new patented medicine in Canada is compared with list prices in seven countries: France, Germany, Italy, Sweden, Switzerland, the United Kingdom, and the United States. Depending on advice from a clinical advisory committee, new medicines are categorized into breakthrough medicines or medicines that provide a substantial, moderate, or slight/no improvement over existing therapies. The ceiling list price for breakthrough medicines is the median of the list prices in the comparator countries; progressively lower ceiling prices are set for the other categories.

In the proposed changes (Acri, 2018, 2022; Rawson, 2018b, 2019b, 2020c; Rawson and Adams, 2019; Rawson and Barua, 2017; Skinner and Rawson, 2020), Switzerland and the United States, countries with generally higher drug prices, would be replaced with six countries (Australia, Belgium, Japan, Netherlands, Norway and Spain) that, on average, have lower list prices. The PMPRB would also use HTAs and economic tests based on Canada's per-capita gross domestic product and the value of the drug's sales in Canada to regulate drug prices. Additionally, manufacturers would be compelled to report confidential information about rebates negotiated with insurers to the PMPRB. The PMPRB would have been converted from a patent-abuse watchdog into a price setter, and prices of new medicines in Canada drastically reduced to a level unsustainable for drug developers (Rawson, 2018b; Rawson and Lawrence, 2020).

The planned PMPRB changes caused much uncertainty and opposition among drug developers and profound concern among patients. Almost all patients, individually and in groups, submitting briefs to the House of Commons Standing Committee on Health hearing on the changes expressed concerns about their impact on access (Rawson and Adams, 2021b). Legal challenges by manufacturers led to courts striking down the use of HTAs and the other economic factors to set prices and the requirement to reveal business secrets. The courts found that the PMPRB had abused its existing powers and that the proposed changes would lead to trespass by the federal government into provincial jurisdiction over property and civil rights including drug prices (Rawson and Adams, 2021c).

The PMPRB's role begins when a new patented medicine is sold for the first time in Canada, whether it is paid for by public or private insurance or directly by a patient. By the first sale, most drug developers have a target Canadian list price in mind based on factors that include investments made in the drug's research and development program, costs of manufacturing, distributing, and promoting the medicine, and any patient support program. An assessment is made before the first sale in Canada to determine whether the target Canadian list price will be PMPRB-compliant. If not, the manufacturer must decide whether to decrease its price to achieve compliance, keep the price and risk action by the PMPRB against the company, delay launching in Canada or not launch at all. If it has already been launched at a price eventually found not to be PMPRB-compliant, this raises difficulties for the Canadian company and possibly conflict with its global office.

When the federal government's actions result in the Canadian market being viewed with uncertainty, or worse pessimism, by international pharmaceutical businesses, Canadian affiliates are placed in a weak position when trying to attract investment from their head offices, resulting in research and manufacturing capacity often going to more collaborative countries (Lucas, 2020). They also have to compete to bring new medicines to Canada. Uncertainty around whether a new drug's price will be PMPRB-compliant places Canadian companies at a disadvantage when global executives develop their priority list of countries for the launch of a new medicine.

In April 2022, the federal cabinet cancelled almost all the proposed revisions, with the principal remaining change being in the countries in the PMPRB's price reference test, a change implemented on July 1, 2022 under a "status quo" approach (PMPRB 2022a). However, the PMPRB and the federal government have not relinquished their objective of reducing drug prices in this country (Rawson and Adams, 2022a), which became clear with the release of new draft PMPRB guidelines in October 2022 for public consultation (PMPRB, 2022b). Eighty-eight submissions were received

in the consultation process, with all but two opposing the changes and raising concerns. In December, the government announced that these guidelines would not be implemented in January 2023 and that the interim guidance would remain in place until further notice.

Opposition to the changes was not surprising. The proposed guidelines were vague, perhaps deliberately so to obfuscate what the PMPRB intended doing. The level of therapeutic improvement or innovation would not be recognized (a change from the previous rules) and prices would be subject to an uncertain or “floating” maximum list price set at the medium of the new 11 comparator countries. Decisions on appropriate comparator medicines would have been decided primarily by PMPRB staff (not its advisory committee) and the PMPRB’s focus would have been the threat of an investigation if a manufacturer’s list price is not considered to be low enough by the PMPRB. Regular reassessments could have been imposed with every new indication for a medicine, new sales of medicines in other jurisdictions, and fluctuating currency exchange rates. Thus, the acknowledgment that a higher price is appropriate for an innovative medicine would have generally been ignored and the emphasis would have been on driving down drug prices, despite a clear court ruling in July 2021 that the PMPRB’s role is to prevent time-limited, patent protection monopolies from being abused by excessive prices and not to set prices by helping itself to powers it does not lawfully have (*Alexion Pharmaceuticals Inc. v. Canada*, 2021).

Companies would not only have had to consider whether a new medicine’s price was PMPRB-compliant at launch but also whether it was likely to be compliant over its patent life because prices would have been benchmarked annually, leading to continuing uncertainty among drug developers about the prices they could charge in Canada. Uncertainty about how prices would have been regulated not only at launch but subsequently makes the risk of launching untenable from both financial and corporate perspectives. Despite the cancellation of the latest proposed guidelines, it seems highly likely that manufacturers will continue to wait-and-see before launching in Canada (Rawson, Abunassar, and Lawrence, 2022). This has already occurred (Martell, 2020; Mungal, 2022; Rawson, 2023). If manufacturers commonly make this decision, submissions of new medicines in Canada will, at best, be delayed longer than they already are (Barua and Esmail, 2013; Rawson, 2018a) and, at worst, not happen, which will affect all Canadians.

Conclusion

Several reasons for later submission of new medicines for marketing authorization exist in Canada, including the country's relatively small and widely dispersed population. However, the principal reason is impediments erected by federal, provincial, and territorial governments that delay marketing and patients' access. These hurdles diminish Canada's desirability as a marketplace for new medicines. In a recent project to develop a biopharmaceutical ecosystem index to assess the ranking of Canada's attractiveness for new medicine launches, the top five concerns were HTA processes, price regulation, intellectual property protection, the market potential, and the market authorization process (Abunassar, Dowson, Fleming, Loschmann, Scott, and Burt, 2022).

Virtually all brand-name pharmaceutical companies in Canada are affiliates of manufacturers based in the United States, Europe, Japan, or other industrialized countries. They have to compete with counterparts in countries round the world to attract not only investment in research, development, and manufacturing but also in launching new medicines. Any disincentive that impedes the process of marketing and getting new medicines to patients, whether that is delays in gaining a recommendation for insurance coverage, price control, price negotiation, or overly restrictive conditions on patient access via public or private insurance, diminishes Canada's attractiveness for launching a new drug, which is first manifested in later submission for marketing authorization.

Manufacturers are unlikely to consistently submit regulatory applications to Health Canada at the same time as they submit to the FDA and the EMA because Canada represents a much smaller market. However, the introduction of incentives in the regulatory process, intellectual property protection consistent with global standards, less confrontational processes for HTA, price negotiation, and price control, and more willing acceptance by provinces to cover new medicines would go a long way to ensuring that applications for marketing authorization are not submitted even later than they are at present. All these hurdles decrease Canada's attractiveness as a market for new medicines. When drug developers decide that launching drugs in Canada is not worthwhile or delay submissions to Health Canada until after launching in other countries, patient suffering is extended and lives are lost.

Access to innovative medicines will be at risk as long as policy makers see new medicines in terms of high prices and not the benefits they can bring to patients, the health-care system, and society. Government policy towards new innovative medicines needs to change from the present obsessive emphasis on cost-containment (Woo, 2022) and other access-restricting actions to reviving biopharmaceutical innovation, research, and manufacturing and ensuring patient access (Rawson and Adams, 2021a, 2022b). Further delays in access or complete denials of access to innovative medicines will hurt even more Canadians with unmet or poorly met health needs that could be helped by new medicines.

References

Abunassar, C., J.P. Dowson, M. Fleming, C. Loschmann, V. Scott, and M. Burt (2022). *Biopharmaceutical Ecosystem Index: Where Does Canada Rank on Its Attractiveness for New Medicine Launch?* PDCI Market Access. <<https://www.pdci.ca/wp-content/uploads/2022/06/PDCI-Biopharmaceutical-Ecosystem-Index-June-2022.pdf>>, as of November 15, 2022.

Acri, Kristina M.L. (2018). *Implications of the Proposed Changes to Canada’s Pharmaceutical Pricing Regulations*. Fraser Institute. <<https://www.fraserinstitute.org/studies/implications-of-the-proposed-changes-to-canadas-pharmaceutical-pricing-regulations>>, as of November 15, 2022.

Acri, Kristina M.L. (2022). *An Evaluation of the Proposed PMPRB Amendments*. Fraser Institute. <<https://www.fraserinstitute.org/studies/an-evaluation-of-the-proposed-pmprb-amendments>>, as of November 15, 2022.

Alexion Pharmaceuticals Inc. v. Canada (2021). Federal Court of Appeal Decisions, 2021 FCA 157 (July 29, 2021). <<https://decisions.fca-caf.gc.ca/fca-caf/decisions/en/item/500849/index.do>>, as of November 15, 2022.

Auditor General of Canada (1987). *Report to the House of Commons, fiscal year ending 31 March 1987*. Supply and Services Canada.

Barua, Bacchus, and Nadeem Esmail (2013). *The Case for Mutual Recognition of Drug Approvals*. Fraser Institute. <<https://www.fraserinstitute.org/sites/default/files/case-for-mutual-recognition-of-drug-approvals.pdf>>, as of November 15, 2022.

Barua, Bacchus, Will Westcott, and Van Nghiem Vo (2021). *Timely Access to New Pharmaceuticals in Canada, the United States, and the European Union*. Fraser Institute. <<https://www.fraserinstitute.org/sites/default/files/timely-access-to-new-pharmaceuticals-in-canada-US-and-EU.pdf>>, as of November 15, 2022.

Begovic, Maja (2022). *Getting Sick to Get Better: Cystic Fibrosis Patients Worry about Access to “Breakthrough” Drug*. Healthing (October 5). <<https://www.healthing.ca/diseases-and-conditions/cystic-fibrosis/trikafta-cystic-fibrosis-drug-access>>, as of November 15, 2022.

Bucher H.C., G.H. Guyatt, L.E. Griffith, and S.D. Walter (1997). The Results of Direct and Indirect Treatment Comparisons in Meta-Analysis of Randomized Controlled Trials. *J Clin Epidemiol* 50: 683–691.

Canadian Agency for Drugs and Technologies in Health [CADTH] (2013). *CDEC Final Recommendation: Eculizumab*. CADTH. <https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Soliris-aHUS_July-23-13.pdf>, as of November 15, 2022.

Canadian Agency for Drugs and Technologies in Health [CADTH] (2022a). *About CADTH*. CADTH. <<https://www.cadth.ca/about-cadth>>, as of November 15, 2022.

Canadian Agency for Drugs and Technologies in Health [CADTH] (2022b). *CADTH Reimbursement Recommendation: Elexacaftor-Tezacaftor-Ivacaftor and Ivacaftor (Trikafta)*. CADTH. <<https://www.cadth.ca/sites/default/files/DRR/2022/SR0710%20Trikafta%20-%20CADTH%20Final%20Rec-meta.pdf>>, as of November 15, 2022.

Cherney, E. (1998). Canadian Viagra sales possible by March. *National Post* (December 22): A4.

Conti, R.M., R. G. Frank, and J. Gruber (2021). Regulating Drug Prices while Increasing Innovation. *N Engl J Med* 385: 1921–1923.

Cooke, A. (2020). “Heartbreaking” death of cystic fibrosis patient shines light on drug access issues. *CBC News* (February 21). <<https://www.cbc.ca/news/canada/nova-scotia/chantelle-lindsay-cystic-fibrosis-death-canada-drug-access-1.5471605>>, as of November 15, 2022.

Downing, N.S., J.A. Aminawung, N.D. Shah, J.B. Braunstein, H.D. Krumholz, and J. S. Ross (2012). Regulatory Review Of Novel Therapeutics – Comparison of Three Regulatory Agencies. *N Engl J Med* 366: 2284–2293.

Eastman, H.C. (1985). *Report of the Commission of Inquiry on the Pharmaceutical Industry*. Supply and Services Canada.

Gagnon, D. (1992). *Working in Partnerships ... Drug Review for the Future*. Health and Welfare Canada.

Goodman, C.S. (2020). M. Managing Individual Bias and Conflict of Interest. *HTA 101: X. Selected Issues in HTA*. National Library of Medicine. <<https://www.nlm.nih.gov/nichsr/hta101/ta101012.html#Heading13>>, as of November 15, 2022.

Grosse, S.D. (2008). Assessing cost-effectiveness in healthcare: history of the \$50,000 threshold. *Expert Rev Pharmacoecon Outcomes Res* 8: 165–178.

Kondro, W. (2002). Drug approvals taking too long? *CMAJ* 166: 790.

Lichtenberg, F.R. (2019). *How Many Life-Years Have New Drugs Saved? A 3-Way Fixed-Effects Analysis of 66 Diseases in 27 Countries, 2000-2013*. Working paper 25483. National Bureau of Economic Research. <https://www.nber.org/system/files/working_papers/w25483/w25483.pdf>, as of November 15, 2022.

Lucas, P. (2020). Canada's vaccine development capacity and the federal government's management of COVID-19. *Canadian Health Policy* (December). <<https://www.canadianhealthpolicy.com/product/canada-s-vaccine-development-capacity-and-the-federal-government-s-management-of-covid-19-2/>>, as of November 15, 2022.

Lybecker, Kristina M. (2017). *Intellectual Property Rights Protection and the Biopharmaceutical Industry: How Canada Measures Up*. Fraser Institute. <<https://www.fraserinstitute.org/sites/default/files/intellectual-property-rights-protection-and-the%20biopharmaceutical-industry.pdf>>, as of November 15, 2022.

Martell, Allison (2020). Exclusive: Canadian regulator considers changes to new drug pricing plan. *Reuters* (February 20). <https://news.yahoo.com/exclusive-canadian-regulator-considers-changes-184639667.html?fr=sycsrp_catchall>, as of November 15, 2022.

Mungal, Penny (2022). Is Canada losing its status as a priority medicine launch country? *Life Sciences Ontario*. <https://lifesciencesontario.ca/is-canada-losing-its-status-as-a-priority-medicine-launch-country-preview_id6648preview_nonce0772186744previewtrue/>, as of November 15, 2022.

National Council on Disability (2019). *Quality-Adjusted Life Years and the Devaluation of Life with Disability*. National Council on Disability (November 6). <https://ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf>, as of November 15, 2022.

National Institute for Health and Care Excellence [NICE] (2015). *Eculizumab for Treating Atypical Hemolytic Uremic Syndrome*. National Institute for Health and Care Excellence. <<https://www.nice.org.uk/guidance/hst1/resources/eculizumab-for-treating-atypical-haemolytic-uraemic-syndrome-pdf-1394895848389>>, as of November 15, 2022.

Overstreet, R.E., J. Berger, and C. Turriff (1989). *Program Evaluation Study of the Drug Safety, Quality and Efficacy Program*. Health and Welfare Canada.

Owens, R.C. (2017). *Defending Our Rights: Eliminating Dysfunction in Canada's Intellectual Property Regime*. Macdonald-Laurier Institute. <https://macdonaldlaurier.ca/mli-files/pdf/MLI_IPPaper3_06-17_webready.pdf>, as of November 15, 2022.

pan-Canadian Pharmaceutical Alliance [pCPA] (2022). *The Negotiation Process*. pCPA. <<https://www.pcpacanada.ca/negotiation-process>>, as of November 15, 2022.

Patented Medicine Prices Review Board [PMPRB] (2022a). *Notice and Comment – PMPRB Price Review Approach during the Interim Period following Publication of Amendments to the Patented Medicines Regulations*. Government of Canada. <<https://www.canada.ca/en/patented-medicine-prices-review/services/consultations/notice-comment-price-review-approach.html>>, as of November 15, 2022.

Patented Medicine Prices Review Board [PMPRB] (2022b). *PMPRB Draft Guidelines 2022*. Patented Medicine Prices Review Board. <<https://www.canada.ca/en/patented-medicine-prices-review/services/consultations/2022-proposed-updates-guidelines.html>>, as of November 15, 2022.

Paul, D. (2001). Comparison of the Drug Approval Processes in the US, the EU and Canada. *Int J Med Marketing* 1: 224–235.

Peterson, R.G. (2002). Response to Commentary. *Pharmacoepidemiol Drug Saf* 11: 341–342.

Pettitt, D.A., S. Raza, B. Naughton, A. Roscoe, A. Ramakrishnan, A. Ali, B. Davies, S. Dopson, G. Hollander, J.A. Smith, and D.A. Brindley (2016). The Limitations of QALY: A Literature Review. *J Stem Cell Res Ther* 6: 4.

PricewaterhouseCoopers (1999). *Therapeutic Products Program: Baseline Assessment of Drug Submission Review Process*. PricewaterhouseCoopers.

Prieto L., and J.A. Sacristán (2003). Problems and Solutions in Calculating Quality-Adjusted Life Years (QALYs). *Health Qual Life Outcomes* 1: 80.

Rawson, Nigel S.B. (2000). Time Required for Approval of New Drugs in Canada, Australia, Sweden, the United Kingdom and the United States in 1996-1998. *CMAJ* 162: 501–504.

Rawson, Nigel S.B. (2002). Human Resources for the Approval of New Drugs in Canada, Australia, Sweden, the United Kingdom and the United States. *Can J Clin Pharmacol* 9: 73–78.

Rawson, Nigel S.B. (2003). Timeliness of Review and Approval of New Drugs in Canada from 1999 through 2001: Is Progress Being Made? *Clin Ther* 25: 1203–1247.

Rawson, Nigel S.B. (2018a). Canadian, European and United States New Drug Approval Times Now Relatively Similar. *Regul Toxicol Pharmacol* 96: 121–126.

Rawson, Nigel S.B. (2018b). New Patented Medicine Regulations in Canada: Case Study of a Manufacturer’s Decision-Making about Regulatory Submission for a Rare Disorder Treatment. *Canadian Health Policy* (October). <<https://www.canadianhealthpolicy.com/product/new-patented-medicine-regulations-in-canada-case-study-of-a-manufacturer-s-decision-making-2/>>, as of November 15, 2022.

Rawson, Nigel (2019a). Pan-Canadian Pharmaceutical Alliance Lacks Transparency and Accountability. Macdonald-Laurier Institute. <<https://macdonaldlaurier.ca/pan-canadian-pharmaceutical-alliance-lacks-transparency-accountability-nigel-lawson-inside-policy/>>, as of November 15, 2022.

Rawson, Nigel (2019b). Proposed new drug regulations will hurt all Canadians – and Ottawa has been warned. *Financial Post* Aug 13. <<https://financialpost.com/opinion/proposed-new-drug-regulations-will-hurt-all-canadians-and-ottawa-has-been-warned>>, as of November 15, 2022.

Rawson, Nigel S.B. (2020a). Alignment of Health Technology Assessments and Price Negotiations for New Drugs for Rare Disorders in Canada: Does It Lead to Improved Patient Access? *J Popul Ther Clin Pharmacol* 27: e48–e64.

Rawson, Nigel S.B. (2020b). Leading Causes of Mortality and Prescription Drug Coverage in Canada and New Zealand. *Front Public Health* 8: 544835.

Rawson, Nigel S.B. (2020c). *The Patented Medicine Prices Review Board Is Selling Canadians a Lemon*. Macdonald-Laurier Institute. <<https://macdonaldlaurier.ca/is-the-patented-medicine-prices-review-board-selling-canadians-a-lemon-nigel-lawson-for-inside-policy/>>, as of November 15, 2022.

Rawson, Nigel S.B. (2021). Health Technology Assessment Standards and Practices: How Does Canada Compare with Other Countries? *Canadian Health Policy* (February 25). <<https://www.canadianhealthpolicy.com/product/health-technology-assessment-standards-and-practices-how-does-canada-compare-with-other-countries-2/>>, as of November 15, 2022.

Rawson, Nigel S.B. (2022). Health Technology Assessment and Price Negotiation Alignment for Rare Disorder Drugs in Canada: Who Benefits? *Orphanet J Rare Dis* 17: 218.

Rawson, Nigel S.B. (2023). *Canada Falls Behind in New Drug Submissions Compared with the United States and Europe*. Canadian Health Policy (January 17). <<https://www.canadianhealthpolicy.com/product/canada-falls-behind-in-new-drug-submissions-compared-with-the-united-states-and-europe/>>, as of March 27, 2023.

Rawson, Nigel S.B, C. Abunassar, and D. Lawrence (2022). *Effect of Amended Patented Medicines Regulations on Industry Decisions to Launch New Drugs in Canada*. Canadian Health Policy Institute (July 13). <<https://www.canadianhealthpolicy.com/product/effect-of-amended-patented-medicine-regulations-on-industry-decisions-to-launch-new-drugs-in-canada/>>, as of November 15, 2022.

Rawson, Nigel S.B., and J. Adams (2017). Do Reimbursement Recommendation Processes Used by Government Drug Plans in Canada Adhere to Good Governance Principles? *Clinicoecon Outcomes Res* 9: 721–730.

Rawson, Nigel S.B., and J. Adams (2019). New rules will keep the best medications from desperate Canadians. *Financial Post* (September 12). <<https://financialpost.com/opinion/new-rules-will-keep-the-best-medications-from-desperate-canadians>>.

Rawson, Nigel S.B., and J. Adams (2021a). More than a Dose of Collaboration: What Ottawa Should Do if It Wants Drugs and Vaccines to Be Made in Canada and Benefit Patients. Macdonald-Laurier Institute. <https://macdonaldlaurier.ca/mlifiles/pdf/20210525_More_than_a_dose_of_collaboration_Rawson_Adams_PAPER_FWeb.pdf?mc_cid=44923e3a19&mc_eid=UNIQID>, as of November 15, 2022.

Rawson, Nigel S.B., and J. Adams (2021b). Use COVID pause to reconsider drug-price regulation. *Financial Post* (January 18). <<https://financialpost.com/opinion/opinion-use-covid-pause-to-reconsider-drug-price-regulation>>, as of November 15, 2022.

Rawson, Nigel S.B., and J. Adams (2021c). Appeal court exposes PMPRB abuse of power and bias on drug pricing. *Financial Post* (August 18). <<https://financialpost.com/opinion/opinion-appeal-court-exposes-pmprb-abuse-of-power-and-bias-on-drug-pricing>>, as of November 15, 2022.

Rawson, Nigel S.B., and J. Adams (2022a). Liberal's PMPRB scale-back not a "win" for Big Pharma or patients. *National Newswatch* (May 24). <<https://www.nationalnewswatch.com/2022/05/24/liberals-pmprb-scale-back-not-a-win-for-big-pharma-or-patients/#:YvgkrXbMKM>>, as of November 15, 2022.

Rawson, Nigel S.B., and J. Adams (2022b). *Ottawa Should Reset Its Relationship with Drug Developers to Improve Patient Health*. Macdonald-Laurier Institute (May 2). <<https://macdonaldlaurier.ca/ottawa-should-reset-its-relationship-with-drug-developers-to-improve-patient-health-rawson-and-adams-for-inside-policy/>>, as of November 15, 2022.

Rawson, Nigel, and Bacchus Barua (2017). Changes could reduce access to medications. *Winnipeg Free Press* (July 6). <<https://www.winnipegfreepress.com/opinion/analysis/2017/07/06/changes-could-reduce-access-to-medications>>, as of November 15, 2022.

Rawson, Nigel S.B., K.I. Kaitin, K.E. Thomas, and G. Perry (1998). Drug Review in Canada: A Comparison with Australia, Sweden, the United Kingdom and the United States. *Drug Inform J* 32: 1133–1141.

Rawson, Nigel S.B., and D. Lawrence (2020). New Patented Medicine Regulations in Canada: Updated Case Study of a Manufacturer's Decision-Making about Regulatory Submission for a Rare Disorder Treatment. *Canadian Health Policy* (January 1). <<https://www.canadianhealthpolicy.com/product/new-patented-medicine-regulations-in-canada-updated-case-study-en-fr-2/>>, as of November 15, 2022.

Richter, T., G. Janoudi, W. Amegatse, and S. Nester-Parr (2018). Characteristics of Drugs for Ultra-Rare Diseases versus Drugs for Other Rare Diseases in HTA Submissions Made for the CADTH CDR. *Orphanet J Rare Dis* 13: 15.

Richter, T., and K.M. Lee (2015). *Guidance Document on Reporting Indirect Comparisons*. CADTH. <https://www.cadth.ca/sites/default/files/pdf/MH0003_Guidance_on_IDC_Reporting.pdf>, as of November 15, 2022.

- Rowen, D., I. Azzabi Zouraq, H. Chevrou-Severac, and B. van Hout (2017). International Regulations and Recommendations for Utility Data for Health Technology Assessment. *Pharmacoeconomics* 35: 11–19.
- Shajarizadeh, A., and A. Hollis (2015). Delays in the Submission of New Drugs in Canada. *CMAJ* 187: E47–E51.
- Skinner, Brett, and Nigel Rawson (2020). Extreme regulations to lower drug prices mean Canada will get fewer new drugs. *Financial Post* (February 7). <<https://financialpost.com/opinion/extreme-regulations-to-lower-drug-prices-mean-canada-will-get-fewer-new-drugs#comments-area>>, as of November 15, 2022.
- Stroud, R. (1995). *Drug Submission Evaluation: International Comparison of Performance Standards and Performance*. Health Canada.
- Tandon, P.K., and E.D. Kakkis (2021). The Multi-Domain Responder Index: A Novel Analysis Tool to Capture a Broader Assessment of Clinical Benefit in Heterogeneous Complex Rare Diseases. *Orphanet J Rare Dis* 16: 183.
- Ward, L.M., A. Chambers, E. Mechichi, D. Wong-Rieger, and C. Campbell (2022). An International Comparative Analysis of Public Reimbursement of Orphan Drugs in Canadian Provinces Compared to European Countries. *Orphanet J Rare Dis* 17: 113.
- Wells, Paul (2021). Trudeau and Big Pharma: Not a Love Story. *Macleans's* (February 22). <<https://www.macleans.ca/politics/ottawa/trudeau-and-big-pharma-not-a-love-story/>>, as of November 15, 2022.
- Wong-Rieger, D. (2022). *CORD Open Letter to Premiers*. Canadian Organization for Rare Disorders (July 8). <<https://www.raredisorders.ca/cord-open-letter-to-premiers/>>.
- Woo, A. (2022). Past presidents of BC Cancer says *[sic]* priority shift to fiscal management weighed on agency's decline. *Globe and Mail* (October 1). <<https://www.theglobeandmail.com/canada/article-british-columbia-cancer-care/>>, as of November 15, 2022.
- Working Group on Drug Submission Review (1987). *Memorandum to the Minister* (the Stein Report). Health and Welfare Canada.

About the Author

Nigel Rawson

Nigel Rawson is a pharmacoepidemiologist and pharmaceutical policy researcher in Saskatoon, Saskatchewan. Educated in the United Kingdom, he holds an MSc in statistics and a PhD in pharmacoepidemiology. Dr. Rawson has performed epidemiologic studies of the use of drugs and their outcomes for over 40 years and published more than 150 book chapters and articles in peer-reviewed journals. He is also the author of the monograph, *Drug Safety: Problems, Pitfalls and Solutions in Identifying and Evaluating Risk*.



Dr. Rawson held academic research positions in the United Kingdom until the end of 1989 and subsequently held professorships at the University of Saskatchewan and Memorial University of Newfoundland in Canada. His research activities focused on population-based studies of the use and safety of drugs using administrative health-care utilization data and the evaluation of issues affecting access to new drugs. Dr. Rawson has also been a senior researcher in an independent research centre in one of the United States' largest health insurers, where he collaborated with the Food and Drug Administration on drug safety studies; and GlaxoSmithKline's only epidemiologist in Canada, providing advice and analysis for the company's current and developing medicines and vaccines. Between 2012 and 2020, Dr. Rawson was President of Eastlake Research Group whose mission was to create evidence-based responses to pharmaceutical and health-policy issues. He continues this work as an independent researcher.

Acknowledgments

The author wishes to acknowledge the helpful comments and insights of several anonymous reviewers. Any remaining errors or oversights are the sole responsibility of the author. As the researcher has worked independently, the views and conclusions expressed in this study do not necessarily reflect those of the Board of Directors of the Fraser Institute, the staff, or supporters.

Publishing Information

Distribution

These publications are available from <<http://www.fraserinstitute.org>> in Portable Document Format (PDF) and can be read with Adobe Acrobat® or Adobe Reader®, versions 7 or later. Adobe Acrobat Reader® DC, the most recent version, is available free of charge from Adobe Systems Inc. at <<http://get.adobe.com/reader/>>. Readers having trouble viewing or printing our PDF files using applications from other manufacturers (e.g., Apple's Preview) should use Reader® or Acrobat®.

Ordering publications

To order printed publications from the Fraser Institute, please contact us via e-mail: sales@fraserinstitute.org; telephone: 604.688.0221, ext. 580 or, toll free, 1.800.665.3558, ext. 580; or fax: 604.688.8539.

Media

For media enquiries, please contact our communications department via e-mail: communications@fraserinstitute.org; telephone: 604.714.4582.

Copyright

Copyright © 2023 by the Fraser Institute. All rights reserved. No part of this publication may be reproduced in any manner whatsoever without written permission except in the case of brief passages quoted in critical articles and reviews.

ISBN

978-0-88975-732-5

Citation

Nigel S.B. Rawson (2023). *Waiting for New Medicines: How Does Canada Compare to the United States and Europe?* Fraser Institute. <<http://www.fraserinstitute.org>>.

Supporting the Fraser Institute

To learn how to support the Fraser Institute, please contact us via post: Development Department, Fraser Institute, Fourth Floor, 1770 Burrard Street, Vancouver, British Columbia, V6J 3G7, Canada; telephone: toll-free to 1.800.665.3558, ext. 548; e-mail: development@fraserinstitute.org; or visit our webpage: <http://www.fraserinstitute.org/support-us/overview.aspx>.

Purpose, Funding, and Independence

The Fraser Institute provides a useful public service. We report objective information about the economic and social effects of current public policies, and we offer evidence-based research and education about policy options that can improve the quality of life.

The Institute is a non-profit organization. Our activities are funded by charitable donations, unrestricted grants, ticket sales, and sponsorships from events, the licensing of products for public distribution, and the sale of publications.

All research is subject to rigorous review by external experts, and is conducted and published separately from the Institute's Board of Directors and its donors.

The opinions expressed by authors are their own, and do not necessarily reflect those of the Institute, its Board of Directors, its donors and supporters, or its staff. This publication in no way implies that the Fraser Institute, its directors, or staff are in favour of, or oppose the passage of, any bill; or that they support or oppose any particular political party or candidate.

As a healthy part of public discussion among fellow citizens who desire to improve the lives of people through better public policy, the Institute welcomes evidence-focused scrutiny of the research we publish, including verification of data sources, replication of analytical methods, and intelligent debate about the practical effects of policy recommendations.

About the Fraser Institute

Our mission is to improve the quality of life for Canadians, their families and future generations by studying, measuring and broadly communicating the effects of government policies, entrepreneurship and choice on their well-being.

Notre mission consiste à améliorer la qualité de vie des Canadiens et des générations à venir en étudiant, en mesurant et en diffusant les effets des politiques gouvernementales, de l'entrepreneuriat et des choix sur leur bien-être.

Peer review—validating the accuracy of our research

The Fraser Institute maintains a rigorous peer review process for its research. New research, major research projects, and substantively modified research conducted by the Fraser Institute are reviewed by experts with a recognized expertise in the topic area being addressed. Whenever possible, external review is a blind process. Updates to previously reviewed research or new editions of previously reviewed research are not reviewed unless the update includes substantive or material changes in the methodology.

The review process is overseen by the directors of the Institute's research departments who are responsible for ensuring all research published by the Institute passes through the appropriate peer review. If a dispute about the recommendations of the reviewers should arise during the Institute's peer review process, the Institute has an Editorial Advisory Board, a panel of scholars from Canada, the United States, and Europe to whom it can turn for help in resolving the dispute.

Editorial Advisory Board

Members

Prof. Terry L. Anderson

Prof. Herbert G. Grubel

Prof. Robert Barro

Prof. James Gwartney

Prof. Jean-Pierre Centi

Prof. Ronald W. Jones

Prof. John Chant

Dr. Jerry Jordan

Prof. Bev Dahlby

Prof. Ross McKittrick

Prof. Erwin Diewert

Prof. Michael Parkin

Prof. Stephen Easton

Prof. Friedrich Schneider

Prof. J.C. Herbert Emery

Prof. Lawrence B. Smith

Prof. Jack L. Granatstein

Dr. Vito Tanzi

Past members

Prof. Armen Alchian*

Prof. F.G. Pennance*

Prof. Michael Bliss*

Prof. George Stigler*†

Prof. James M. Buchanan*†

Sir Alan Walters*

Prof. Friedrich A. Hayek*†

Prof. Edwin G. West*

Prof. H.G. Johnson*

* deceased; † Nobel Laureate