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Timely Access to New Pharmaceuticals in Canada, the United States, and the European Union

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Executive Summary

Modern medicines not only treat illnesses that could not previously be treated, but also represent a substitution for older, less efficient, and less effective methods of treatment. Newer medicines can expand access to better health through reductions in adverse events and reactions, and may work better for some parts of the population poorly served by previous advances. Access to these newer (and potentially superior) drugs, however, is not equal across developed countries.

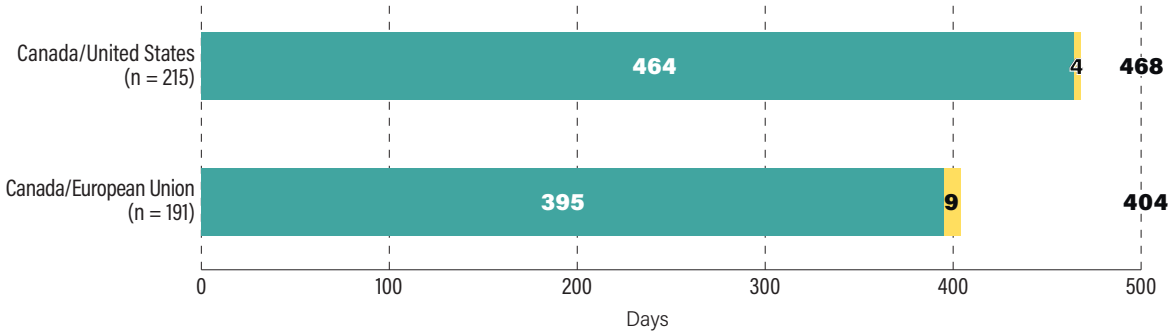
New medicines are only accessible by the public after they have been granted regulatory clearance by a jurisdiction's responsible body, such as Health Canada, the United States Food and Drug Administration (FDA), and the European Medicines Agency (EMA). Past studies have shown that Health Canada both takes longer to approve medicines (from the time of submission) and approves fewer medicines than its American and European counterparts.

However, a delay in the availability of new drugs in one country in comparison with another can have two sources: a difference in approval time (efficiency) and a difference in when the drug was submitted for approval in the first place. In order to capture the total delay in timely access to new medicines, this study undertakes a drug-by-drug comparison for dates of approval granted by Health Canada, the FDA, and the EMA (including both the European Union's centralized approval procedure and its mutual recognition approach). We seek to measure the differences between when populations served by these agencies were ultimately granted access to new pharmaceutical products and therapies.

We find considerable delays in the approval of new medicines in Canada in comparison with access in the United States and Europe. Of the 218 drugs approved in both Canada and the United States between 2012/13 and 2018/19, approval was granted a median 289 (average 469) days earlier in the United States. Of the 205 drugs approved in both Canada and Europe, approval was granted a median 154 (average 468) days earlier in Europe. The more important factor in explaining these delays in approval of new medicines in Canada is the difference in the dates on which manufacturers submitted new drugs to agencies for regulatory approval.

If we constrain our analysis to compare drugs for which submission dates are available, the average 468-day difference in approval dates between Canada and the United States (for 215 drugs) consists of an average 464-day difference between submission dates, and

Average difference (days) in submission and efficiency in the United States and the European Union compared to Canada, 2012/13–2018/19



Note: Totals may not add up as a result of rounding.

an average 4-day difference in efficiency. Similarly, the average 404-day difference in approval dates between Canada and Europe (for 191 drugs) consists of an average 395-day difference between submission dates, and an average 9-day difference in efficiency.

Several reasons for this difference in dates of submission may exist, including differences in market-investment attractiveness because of prevalent intellectual-property protection regimes, the size and sophistication of the potential market of consumers, regulatory controls on drug pricing, and the reimbursement policies practised by public and private insurers. Another reason, more directly related to regulatory activities, is the extra financial burden incurred through user fees and the costs associated with creating a submission for a particular agency.

One way to reduce the loss of potential benefits from earlier (and possibly increased) availability of newer medicines for Canadians, would be to recognize that the approach taken by Health Canada is largely unnecessary. While the potential for harm that accompanies any new medicine on the market may provide justification for regulatory approval in general, Health Canada's approval process largely duplicates what is already being done (about as efficiently, but much earlier) in the United States and Europe, which means the benefits of this process for Canadians are limited at best. Indeed, as David Paul notes, the procedures and requirements of the FDA are the framework for those used in the European Union and Canada.

All of this means that Canadians are denied the health benefits of many medicines for months, if not years, waiting for their government to duplicate approvals already provided in other jurisdictions. Given the low and similar rate of withdrawal of drugs (at least in the United States and Canada), it can be said that this delay is denying Canadians access to many medicines that will ultimately be found sufficiently safe and effective not to be withdrawn from the marketplace. Canadians also, perhaps as

a result of the costs to manufacturers of entering a small and highly regulated market, receive access to fewer medicines in total than their counterparts in other developed nations, leaving Canadians with fewer therapeutic options and potentially worse health outcomes. And, beyond these foregone benefits lie the costs to taxpayers and drug manufacturers of funding this duplicative process.

This provides a strong reason to consider replacing (or augmenting) Health Canada's mandatory approval process with agreements that recognize approval by comparable international agencies. Under such an approach, approval by the FDA or the EMA could be considered sufficient for market access in Canada. If Canada had such agreements with Europe and the United States (accepting approval from either body as equivalent), patients could have received access to 223 new pharmaceutical therapies (of the 224 in our sample) a median 383 (average 742) days earlier. Patients would also likely have received access to many drugs approved by the EMA or FDA but not available in Canada because they were either not approved by Health Canada or were simply not submitted for marketing approval in Canada at all. The clear benefits of this approach would be a reduction in the costs of entry to the Canadian marketplace and a significant reduction in the delay Canadians endure for access to new drugs.

This process can be implemented while maintaining Health Canada's ability to provide safety warnings and to require withdrawal of a drug from the Canadian marketplace, as well as Health Canada's approval process on a non-mandatory basis. Specifically, while approvals by the FDA and EMA could be accepted as sufficient for market entry, they could also be subject to a labeling requirement stating the approval was that of the FDA and EMA and that Health Canada had not approved that particular medicine. This would give Canadians and their health-care providers the opportunity to decide for themselves if they felt Health Canada's approval process provided additional safety or protection from the risks associated with a new drug. In addition, the resources saved through accepting approvals by the FDA or EMA could be in part redirected towards other critical activities such as more active post-market surveillance of drug safety and better communication of the risks associated with certain drugs.

The delayed approval of pharmaceuticals highlighted in this study are particularly concerning at a time when Canada's federal government is considering the introduction of restrictive price controls on new pharmaceuticals. Specifically, new legislation intended to come into effect on July 1, 2021, is targeted towards further limiting prices for new pharmaceuticals in Canada via the Patented Medicine Prices Review Board. To the extent that restrictive price controls may have historically contributed to Canada's relatively delayed and limited access to innovative pharmaceuticals, it is likely that these regulations will further exacerbate the delays identified in this study.

Introduction

Modern medicines improve both health outcomes and quality of life for those stricken with illness; and their ability to do so continues to improve and advance over time. Every day, researchers and scientists work to come up with new and innovative ways to treat illnesses, reduce suffering, and prolong life while research-based pharmaceutical companies invest in the development and testing necessary to bring these innovations to market.

The medicines that are available today are not only able to treat illnesses that could not previously be treated, but also represent a substitution for older, less efficient, and less effective methods of treatment. Even in cases where medicines may not have a different impact therapeutically, they can expand access to better health through reductions in adverse events and reactions, and may work better for some parts of the population poorly served by previous advances.

However, access to these newer (and often superior) pharmaceuticals is not equal across developed countries. This is, in part, the result of governmental regulations and approvals. Critically, new medicines are only accessible to the public after they have been granted regulatory clearance by the host jurisdiction's responsible body such as Health Canada, the United States Food and Drug Administration (FDA), and the European Medicines Agency (EMA). [1] The efficiency with which these agencies approve drugs and the numbers of drugs ultimately approved has historically varied considerably among these regulatory authorities (Rawson, 2012, 2013; Barua and Esmail, 2013; Downing et al., 2012).

Previous studies indicate that Health Canada historically took longer than the FDA or EMA to approve drugs. For example, Skinner and Rovere (2012) found that Health Canada approved drugs slower than the EMA in each of the five years examined between 2006 and 2010, and slower than the FDA in six of the seven years between 2004 and 2010. These differences seem to have diminished over time as more recent studies (*e.g.*, Rawson 2018a) indicate the three jurisdictions approved new drugs with similar efficiency by 2016.

[1] The European Medicines Agency (EMA) is the European Union's agency for regulating and approving pharmaceutical substances.

However, differences in efficiency alone (or differences in the number of new active substances approved in a particular year), while important, do not identify the true relative delay in access to new medicines as they rarely account for the fact that different medicines may have been submitted to these agencies in different years. As a result, patients could receive access to them at disparate points of time, even if the relevant government authorities approved them with comparable efficiency.

With wider availability of data, a different type of analysis of relative delays in drug approvals began towards the beginning of the previous decade. Specifically, Downing *et al.* (2012) and Rawson (2012, 2013) spearheaded drug-by-drug comparisons for dates of approval granted by different health agencies in order to estimate the differences between when populations served by these agencies are ultimately granted access to new pharmaceutical products and therapies.

Indeed, the previous iteration of this study in 2013 (Barua and Esmail, 2013b) was among the first to conduct a Canada-centric drug-by-drug comparison of differences between approval times for drugs approved by Health Canada between 2005 and 2011/12 and the approval times of the FDA and EMA. The study not only measured differences in efficiency, but pioneered the identification of differences in submission dates (rather than efficiency) as the primary contributor to differences in access and made a clear case for the for the recognition of drug approvals by the FDA or EMA whereby decisions by either agency could be considered sufficient for market access in Canada.

While the potential for harm that accompanies any new medicine on the market may provide some justification for regulatory approval in general, there is still a question why such approval is duplicated in one jurisdiction (*e.g.*, Canada) while it is being undertaken in another with comparable standards (*e.g.*, the European Union). Indeed, to the extent submissions to these agencies and their efficiency in approving them vary, such duplication of effort reinforces the unfortunate reality that different drugs are available to patients in different countries at different points in time.

This study updates the previous study by Barua and Esmail (2013b) to measure the difference in access to new medicines that results from duplication of effort in Canada. By compiling a list of new drugs approved in Canada between 2011/12 and 2018/19, and comparing the corresponding approval dates with those in the United States and the European Union, we provide Canadians an estimate of how much sooner these new drugs would have been available to them in the absence of what might be considered an unnecessary regulatory hurdle imposed by Health Canada.

The Importance of Pharmaceutical Consumption and Vintage

The relationship between the use of pharmaceuticals in the treatment of illness and health has been studied extensively. As our brief overview of the literature below demonstrates, pharmaceutical consumption is related to both better health outcomes and increased longevity. Further, newer medicines are linked to superior health outcomes than provided by older medicines. For example, Frech and Miller (1999) found a clear relationship between pharmaceutical expenditure and life expectancy (though not infant mortality). Frech and Miller subsequently updated their analysis and demonstrated further relationships between pharmaceutical consumption and circulatory-disease mortality at all ages, cancer and respiratory disease mortality among the elderly, and quality of life (Miller and Frech, 2002).

Drugs have also been found to play an important role in freeing up other medical resources. For example, while examining whether changes in drug use result in subsequent changes in use of inpatient care and mortality between 1980 and 1992, Lichtenberg (1996) found that increases in the use of prescription drugs were linked to reductions in the number of hospital bed-days consumed.

In 2013, the Conference Board of Canada (Hermus, Stonebridge, Dinh, Didic, and Thériault, 2013) examined the combined health and societal impact of ACE inhibitors (for high blood pressure), statins (for high cholesterol), biguanides (for diabetes), biological response modifiers (for rheumatoid arthritis), inhaled steroids (for asthma), and prescription smoking-cessation aids. Their study found that the $1.22 billion spent on these pharmaceutical treatments in Ontario generated offsetting health and societal benefits of $2.44 billion, and that the net benefits of pharmaceutical spending were positive for each of these drug classes except biologic response modifiers and pharmaceutical smoking-cessation aids. They also projected their findings into the future and found that all six classes of drugs could be expected to produce positive net benefits (health and social benefits greater than drug cost) between 2013 and 2030. In a more recent study (Gagnon-Arpin and Sutherland, 2017), the Conference Board of Canada assessed the economic impact of increasing access to a new medication category—proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i). The study found that increased access to PCSK9i would result in 324 to 12,084 averted deaths for individuals

with heterozygous familial hypercholesterolemia (HeFH) [2] for the forecast period of 2016 to 2035, resulting in total cost savings ranging from $52.3 million to $2.0 billion. Further, in the secondary prevention category, [3] increasing access to PCSK9i was projected to result in 67,901 to 202,689 averted deaths over the forecast period, with cumulative total cost savings estimated between $11.0 billion to $32.8 billion.

While these studies and much of the literature in this area find considerable benefits from drugs generally, a number of peer-reviewed studies by Frank Lichtenberg [4] of Columbia University have further found that the vintage (or novelty) of drugs consumed is also an important factor in generating health and social benefits. [5] For example, Lichtenberg (2012) found that the use of newer drugs was associated with faster increases in life expectancy and survival rates above age 25 in 30 developing and high-income countries between 2000 and 2009. In a more specific example, Lichtenberg (2008) found newer cardiovascular drugs reduced the average length of stay and the age-adjusted cardiovascular mortality rate (though not potential years of life lost) in 20 OECD countries between 1995 and 2004. [6] In a more recent study, Lichtenberg (2019b) analysed the impact of new drugs' disability-adjusted life-years lost (DALY). The study concluded that new drugs introduced between 1986 and 2001 reduced disability-adjusted life-years lost (DALYs) in 2016 by 21%. In a separate study, Lichtenberg (2019a) also determined that, if no new drugs had been launched after 1981, the number of years of life lost before the age of 85 would have been, by the year 2013, 2.16 times higher than it actually was.

Further, newer drugs may have considerable cost savings associated with their use through reductions in the need for other health-care services such as hospital and

[2] A genetic disorder characterized by high LDL-C levels.

[3] Which includes individuals who have already experienced a cardiovascular event such as a heart attack or stroke.

[4] Although Lichtenberg is widely considered to be the leading expert in this area, some authors have challenged his findings. For a critique of Lichtenber's prior studies, see Baker and Fugh-Berman, 2009. Lichtenberg (2009) subsequently responded to this critique directly in an SSRN article.

[5] Vintage or novelty refers not only to newer medicines but also to both incremental and breakthrough improvements. Breakthrough improvements will include those that allow treatment of a previously untreatable condition, or allow medicinal treatment of a condition where the previous approach was invasive. Incremental improvements will be those that have a similar therapeutic effect as an existing medicine but provide some other benefit beyond the existing treatment that serves either to expand treatable populations, increase comfort and thus potentially increase compliance if not at least reduce the burden of treatment, and/or reduce risks and potential side effects.

[6] Specifically, he found (mean estimate) that average length of stay would have been 12% higher and deaths 11% higher if the change in drug vintage (use of newer drugs) had not occurred.

physician care. Lichtenberg's 2008 study, cited above, estimated that per-capita hospital expenditures would have been 70% ($89) higher in 2004 in the absence of improvements in drug vintage. More broadly, in a 2002 study, Lichtenberg found that using newer drugs (reduced vintage) increased prescription costs by $18 per patient in the United States but reduced non-drug spending (primarily hospital and physician spending) by $129 or about 7.2 times as much as the increase in drug spending.

Blankart and Lichtenberg (2020) have also demonstrated that newer drugs correspond with increased adherence, which is the rate at which patients use the medicines prescribed as advised. Specifically, a 10-year increase in the average drug vintage is associated with 2.5% increase in adherence. Non-adherence is estimated to account for an annual preventable cost of $100 billion in the US heath-care system, and it amounts to roughly half of the potentially avoidable cost of inappropriate medication usage.

These studies, both those examining pharmaceuticals generally and those looking at the vintage of medicines consumed, all point to a central conclusion: access to drugs and particularly newer drugs is beneficial to health and well-being and may generate additional benefits for society in terms of net reductions in health-care costs. Thus, it is valuable to judge the performance of Canada's regulatory agency, Health Canada, in its ability to provide timely access to medicines and to assess the drawbacks of duplicative efforts by Health Canada when agencies in jurisdictions with larger populations are already providing reviews of drug safety.

Delays in Access to New Medicines in Canada

The drug approval process—differences in efficiency

After new drugs have passed through the requisite clinical trial process in accordance with basic international scientific standards, [7] governments typically subject them to a mandatory regulatory approval process before allowing them to be sold in their respective countries. In Canada, manufacturers are required to receive a notice of compliance (NOC) indicating that the new drug is considered safe and effective by Health Canada, the agency responsible for approving new pharmaceutical medicines through its Therapeutic Products Directorate (TPD) and new biologic and radiopharmaceutical medicines through its Biologics and Genetic Therapies Directorate (BGTD). A similar function is fulfilled by the FDA in the United States (Thaul, 2012).

In the European Union, manufacturers have a variety of choices for regulatory approval. [8] Through the Centralized Procedure overseen by the EMA, manufacturers can, by virtue of a single application, receive authorization to market a medicine to patients and healthcare professionals throughout the European Economic Area [EEA] (EMA, 2015). Manufacturers may also follow a Mutual Recognition Procedure (seeking authorization in other countries on the basis of previous authorization in a reference country), a National Authorization Procedure for individual countries, or a Decentralized Procedure (applying for simultaneous authorization in multiple countries).

While clinical testing is, broadly speaking, completed under internationally defined processes common across nations, [9] regulatory approval processes are handled with varying approaches and rates of efficiency depending on the government agency involved. Numerous reviews of the efficiency of regulatory agencies have raised important questions about the pace at which Health Canada provides drug approvals.

[7] Such as those established by the World Medical Association Declaration of Helsinki (WMA, 1964).

[8] Some drugs, however, are specifically required to use the centralized procedure. These include "biologic agents or other products made using high-technology procedures ... products for HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions and viral diseases [and] products for orphan conditions" (MaRS, 2010: 1).

[9] While the international scientific standards for clinical trials established by the World Medical Association Declaration of Helsinki (WMA, 1964) are generally interpreted as the minimum global standard, actual standards deter mining the number, length, and rigour of the required clinical trials are set by governments through domestic regulation.

When examining approval dates for 33 new oncology drugs introduced between 2003 and 2011, Rawson (2012) made two important observations. First, fewer drugs were approved in Canada (24) compared to the United States (30) and the European Community (26). Second, the time taken to approve the 24 drugs in Canada (median 356 days) was almost twice as long as the time taken to approve the same drugs in the United States (median 182 days), but slightly less than in the European Union (408 days).

Barua and Esmail (2013a) found that Health Canada took a median of 355 days to issue a notice of compliance [10] for new patented medicines in 2011—10 days faster than the EMA, and 15 days slower than the FDA. However, they also found that between 2007 and 2011 the delay for access to new medicines that Canadians could generally expect was longer than experienced in the European Union for most years during that period and longer than experienced under the FDA for between two and four of the five years studied (depending on whether mean or median approval times are compared).

Downing and his colleagues (2012) examined drug approvals between 2001 and 2010. When including all drugs approved in the three regions during the period studied, they found that, not only did the FDA approve a larger number of drugs (225 novel therapeutic agents, compared to 186 by the EMA, and 99 by Health Canada), but approved them faster than the other two agencies (322 days, compared to 366 by the EMA, and 393 by Health Canada). Further, when the sample was constrained to the 72 products approved in all three regions, the median total review time at the FDA was some 90 to 100 days shorter than at the EMA or Health Canada.

Rawson (2013), in a study comparing drug-approval times and safety warnings in Canada and the United States, found that, of 584 new drugs approved between 1992 and 2011, 554 were approved in the United States, 484 in Canada, and 454 in both countries. The median approval time for the 454 drugs approved in both countries was more than six months shorter in the United States than in Canada, though the median approval time in Canada between 2007 and 2011 moved closer to that in the United States, except for oncology drugs. Rawson also found that 385 of the 454 drugs were submitted to US regulators before Canadian regulators (386 were approved in the United States first), almost half of which had a submission date more than six months before the Canadian submission date. Further, the proportion of drugs submitted in the United States more than six months before Canadian submission and the proportion of drugs approved in the United States more than 6 months before Canadian approval was found to have increased over the study period.

[10] This notice of compliance is from the date the drug manufacturer's application for approval is recorded or filed in the Central Registry of Health Canada's Therapeutic Products Directorate or Biologics and Genetics Therapies Directorate.

More recently, Rawson (2018a) found that between 2002 and 2016 Health Canada approved more drugs (351) than the EMA (319), but fewer than the FDA (392). Similarly, Health Canada approved drugs slightly faster (median 364 days) than the EMA (371 days), but took longer than the FDA (304 days). Another study by Rawson concluded that "the percentage of new drugs approved in Canada before or within a year after approval in the United States decreased substantially from an average between 2013 and 2016 of 55.4% to 15.6% in 2019" (2020: abstract)—a finding further supported by Eccleston (2019) who found that the FDA approved an average of 12 drugs more than Health Canada between 2014 and 2019.

Clearly, in simple comparative terms, although Health Canada historically lagged the EMA in terms of efficiency and the number of drugs approved, recent evidence suggests it has caught up and reversed this trend to a degree. However, Health Canada both approves fewer medicines than the FDA and does so less efficiently.

The true relative delay for access to new medicines

While the topic of efficiency is an important one, it does not provide a true representation of differences among when drugs are eligible for sale in the three regions. Critically, delayed access to new drugs in one country in comparison with another can have two sources: a difference in approval time (efficiency) and a difference in when the drug was submitted for approval in the first place. Thus, comparisons of efficiency are hindered when there is no control for the fact that different medicines may have been submitted to these agencies in different years. As a result, patients could receive access to them at disparate points of time, even if the relevant government authorities approved them with comparable efficiency.

For example, if a medicine was submitted to the FDA or EMA before submission to Health Canada for approval and, if these agencies took the same amount of time to approve the drug, the true relative delay for access to that drug in Canada would be longer than suggested by the measures of efficiency discussed in the previous section. Differences in submission can happen for a number of reasons, including incentives for market entry and the effort required to create a drug submission. As a result, new drugs are submitted by companies to agencies at different times rather than concurrently in all jurisdictions. [11] Whatever the cause of the total delay, the policy issue is the timeliness of access to medicines for Canadians.

[11] It may also be the case that companies do not have the sufficient supply to bring a drug to Canada at the same time as to the larger markets.

Downing and colleagues (2012) briefly touch upon this subject when they note that among those drugs approved in the United States and Canada, 132 (85.7%) were first approved in the United States, with drugs available a median of 355 days earlier there. Similarly, Rawson (2013) finds that 386 of 454 drugs approved in both Canada and the United States were approved first in the United States (where 385 were submitted first), 77% of which (297 drugs) were approved in Canada more than six months after approval in the United States. Rawson also notes the proportion of drugs that were approved in Canada more than six months after they were approved in the United States was higher in the last decade of his study (74.7% from 2001 to 2011) than in the first decade (58.7% from 1992 to 2001). In a previous study, Rawson (2012) found the combined submission and approval delay in Canada resulted in a median delay relative to US approval of 364 days for 21 cancer drugs approved by Health Canada, the FDA, and the EMA between 2003 and 2011. Notably, Canadian approval lagged US approval by more than six months for 19 of the 21 drugs, and by more than 18 months for 9.

In order to capture this important aspect of timely access in more detail, Barua and Esmail's (2013) analysis undertook a drug-by-drug comparison for dates of approval granted by Health Canada, the FDA, and the EMA (including both the centralized approval procedure and the mutual recognition approach) in order to estimate the differences between when populations served by these agencies are ultimately granted access to new pharmaceutical products and therapies. Of the 149 drugs approved in both Canada and the United States between 2005 and 2012, they found that approval was granted a median 350 days earlier in the United States. Of the 146 drugs approved in both Canada and the European Union, approval was granted a median 263 days earlier in the European Union.

The more important factor in explaining these delays in access to medicines in Canada is differences in the dates on which manufacturers submitted new drugs to agencies for regulatory approval. When Barua and Esmail constrained their analysis to compare drugs for which submission dates were available, the average 682-day difference between approval dates in Canada and the United States (for 120 drugs) consisted of an average 635-day difference between submission dates, and an average 48-day difference in efficiency. Similarly, the average 417-day difference between approval dates in Canada and the European Union (for 131 drugs) consists of an average 315-day difference between submission dates, and an average 102-day difference in efficiency.

Again, the recent study by Rawson referred to earlier (2018a) reported that, of the 252 drugs approved by Health Canada, the EMA, and the FDA between 2002 and 2016, 80% were submitted later to Health Canada leading to a true median delay of a year between first approval by the EMA or FDA, and approval by Health Canada.

In order to continue capturing this important aspect of timely access, the analysis in the current study updates Barua and Esmail's report by undertaking a drug-by-drug comparison for dates of approval granted by Health Canada, the FDA, and the EMA (including both the centralized approval procedure and the mutual recognition approach) in order to estimate the differences between when populations served by these agencies are ultimately granted access to new pharmaceutical products and therapies.

Data sources

All data included in this analysis has been drawn from publicly available information from Health Canada's *Annual Drug Submission Performance Reports* (2013, 2014, 2015, 2016, 2017, 2018, 2019), the online *Summary Basis of Decision* (SBD) database (Health Canada, 2020a), the *Notice of Compliance Online Query* (Health Canada, 2020b), and the *Drug Product Database* (2020c). [12] Data for the United States is from the FDA's online searchable catalogue of approved drug products (FDA, 2020). European data is from the *Public Assessment Reports* available on the EMA's online searchable catalogue for drugs approved through the centralized procedure (EMA, 2020) as well as the *Mutual Recognition Product Index* [MRI] (HMA, 2020).

Method

All drugs (therapeutic and biologic) classified as containing new active substances (NASs) [13] that received approval from Health Canada between 2012/13 [14] and 2018/19, and were reported in Canada's *Annual Drug Submission Performance Reports*, were included in our analysis. These drugs were then matched with drugs containing the same active ingredient in the FDA, EMA, and MRI databases. [15]

[12] Small differences (approximately one day, on average) were noted in the approval dates provided in the published *Annual Drug Submission Performance Reports* and Health Canada's online databases, the latter of which displayed some signs of inconsistency depending on the date the authors retrieved the online query. In order to maintain consistency, data is used from the *Annual Drug Submission Performance Reports* wherever possible.

[13] That is, substances containing a medicinal ingredient not previously approved in a drug for sale in Canada, and that is not a variation of a previously approved ingredient such as a salt, ester, enantiomer, solvate or polymorph.

[14] Barua and Esmail's analysis included drugs approved between 2005 and 2011/12. Health Canada shifted from reporting new drug approvals by calendar year to reporting by fiscal year in 2012.

[15] It should be noted that certain drugs considered new active substances in Canada may be considered reformulations of drugs approved previously in other countries.

Following the approach in Downing 2012, drugs classified as Diagnostic Agents (Anatomical Therapeutic Chemical [ATC] code V04), Contrast Media (V08) and Diagnostic Radiopharmaceuticals (V09), were excluded from our analysis, as were disinfectants (D08), Immune sera and Immunoglobulins (J06), Vaccines (J07), and drugs that appeared to be reformulations or variants of previously approved products (though they may not have been classified as such). An additional four pharmaceutical products were excluded from the database because we were unable to clearly identify key regulatory dates, or did not have enough information to perform an exact match (see Appendix B).

The procedure for comparing approval dates is this. Health Canada provides the date that a drug received a Notice of Compliance (NOC), which states that the new drug is in compliance with the regulations and indicates that it is considered by the government agency to be safe and effective. This date is compared to the "Original Approval or Tentative Approval Date" listed on the FDA website. For drugs approved through the centralized procedure in the European Union, the date the Committee for Medicinal Products for Human Use (CHMP), the committee at the EMA responsible for preparing opinions on new human medicines, issued a positive opinion [16] for granting marketing authorization is used. For drugs approved through the mutual recognition procedure in the European Union, the "date of outcome" is used.

It should be noted that this method of analysis is conservative and understates the relative lack of access to medicines in Canada. Our list of drugs is limited to those drugs approved in Canada, and does not include the large quantity of drugs that may have been approved in the United States or the European Union but not Canada. Studies have found that, in the past, fewer drugs have been approved in Canada than in the United States and the European Union (Downing *et al.*, 2012; Rawson, 2012, 2018a). Further, we do not include the considerable delays in provincial listing for reimbursement (Rovere and Skinner, 2012; CHPI, 2018), which is the point at which access to medicines for Canadians reliant on public programs is possible. [17]

[16] Rawson (2012), focusing on delays in patients' access to medicines, uses the number of days between the Marketing Authorization Application and the adoption of the CHMP's opinion by the European Commission (final market authorization) to measure regulatory efficiency. Downing *et al.* (2012) use the date of the CHMP opinion when calculating measures of efficiency instead of the date of final market authorization issued, on the grounds that the latter is an administrative action, taken without regulatory review. As we are examining the substitution of Canadian regulatory review with a recognition agreements with comparable international organizations rather than delays in access for patients in this study, we follow the approach used by Downing *et al.* (2012).

[17] Therefore, the use of the term "access" in this report is limited to the availability of new pharmaceuticals as a result of regulatory approval and does not capture other important aspects of access related to individual financial ability or insurance coverage.

Findings

International differences in patient access to new drugs, 2012/13–2018/19

There were 224 drugs containing new active substances, and matching our inclusion criteria, granted market authorization by Health Canada between 2012/13 and 2018/19. Of these, 218 (97%) were also granted market authorization by the FDA for sale in the United States, while 205 (92%) were granted a positive opinion by the EMA for sale in the European Union (including 14 drugs that were granted authorization in certain EU countries through the mutual recognition procedure). Only one of the 224 drugs (*Sunpreva*) included in our analysis was approved in Canada but not in the United States or the European Union. [18]

Drug approval in Canada and the United States

Of the 218 drugs approved in both Canada and the United States, approval was granted a median 289 (average 469) days earlier in the United States (figure 1). This difference was larger for the 147 pharmaceuticals reviewed by the Therapeutic Products Directorate (TPD) (median 354, average 569 days) and smaller for the 71 biologic therapies reviewed by the Biologics and Genetic Therapies Directorate (BGTD) (median 232, average 261 days).

Drugs granted priority status by Health Canada (58 drugs) were approved a median 245 (average 422) days earlier in the United States, while the 139 subjected to the standard review procedure were approved in Canada a median 356 (average 527) days after receiving approval in the United States. The 21 drugs granted a Notice of Compliance subject to conditions (NOC/c) were approved in Canada a median 257 (average 208) days after receiving approval in the United States.

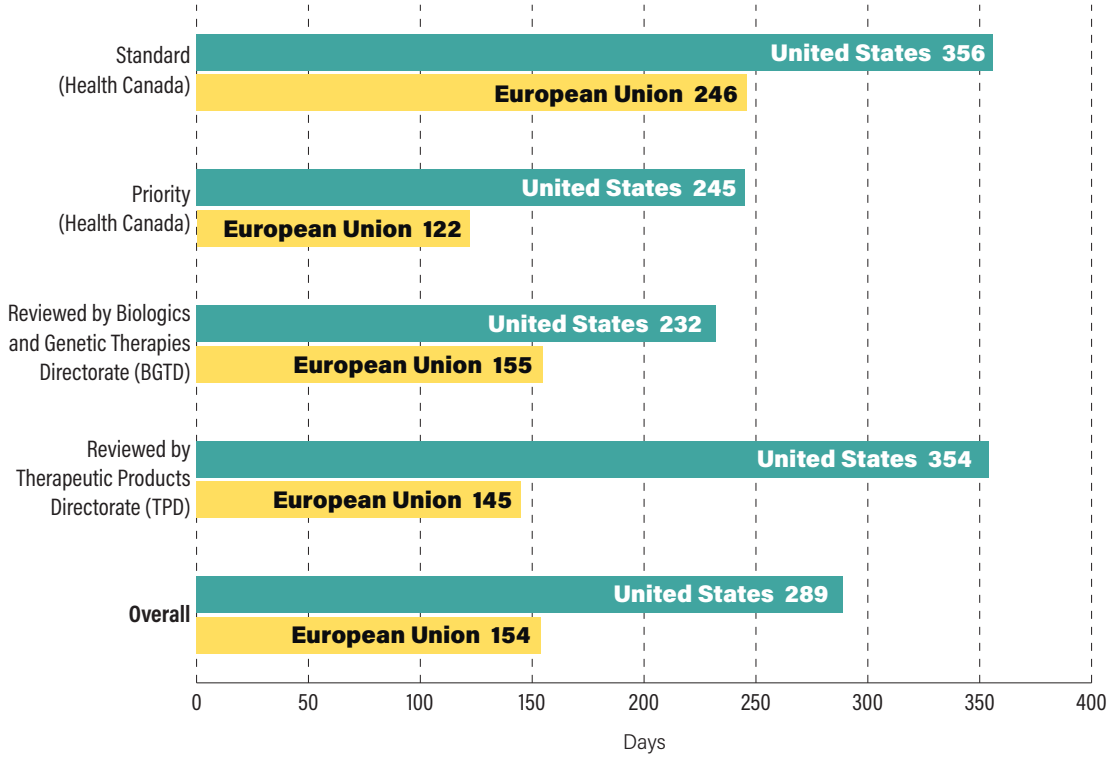
Drug approval in Canada and the European Union

Of the 205 drugs approved in both Canada and the European Union, approval was granted a median 154 (average 468) days earlier in the latter. The median difference was smaller for 134 pharmaceuticals reviewed by the TPD (median 145 days) and larger for the 71 biologic therapies reviewed by the BGTD (median 155 days); the reverse, however, holds true when averages are examined: 519 days for pharmaceuticals reviewed by the TPD and 372 days for the BGTD.

Drugs granted priority status by Health Canada (56 drugs) were approved a median 122 (average 369) days earlier in the European Union, while the 128 subjected to the

[18] *Sunpreva* was later withdrawn from the Canadian market by the manufacturer

Figure 1: 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



standard review procedure were approved in Canada a median 246 (average 565) days after receiving approval in the European Union. The 21 drugs granted a Notice of Compliance subject to conditions (NOC/c) were approved in Canada a median 78 (average 144) days after receiving approval in the United States.

Overall, if we consider first approval in either the European Union or the United States, patients would receive access to 223 new pharmaceutical therapies (of the 224 in our sample), a median 383 (average 742) days earlier. [19] Of these, Health Canada only approved 13 drugs earlier than both the European Union and the United States. Patients would also likely receive access to several drugs approved by the EMA and FDA that were excluded from our sample because they were either not approved by Health Canada or were simply not submitted for marketing approval in Canada in the years examined.

[19] Though considerable, this 383 day delay is smaller than the 494 day delay Barua and Esmail (2013) estimated for the 152 (of 154 drugs in their sample) approved by Health Canada between 2005 and 2011/12.

International differences in patients' access to new drugs, by therapeutic class, 2012/13–2018/19

Using Anatomical Therapeutic Chemical (ATC) codes, it is possible to categorize drugs in our sample by therapeutic class. Table 1 shows the median number of days drugs, by therapeutic class, were approved in the United States (table 1a) and the European Union (table 1b) before they were approved in Canada during the period from 2012/13 to 2018/19.

As seen in tables 1a and 1b, the greatest relative lag between Canadian approval and approval in the European Union is for medicines used to treat sensory organs (780 days); and the shortest lag is for anti-infectives for systemic use (54 days). the greatest relative lag between Canadian approval and approval in the United States is for medicines related to systemic hormonal preparations (excluding sex hormones and insulins) at 775 days, with the shortest difference again in anti-infectives for systemic use (22 days).

International differences in patient's access to new drugs, by year, 2012/13–2018/19

Health Canada approved 38 drugs meeting our inclusion criteria in 2018/19, the most recent year included in our analysis. All 38 of these drugs were also approved in the United States, but were available a median 396 (677 average) days earlier. In the European Union, 32 of the 38 drugs were approved and were available a median 213 (average 534) days earlier (figure 2g). This difference in access is longer than the median 276 (average 145) day disparity with the United States, and the median 163 (average 319) day disparity with the European Union in 2012/13, our first year of analysis. However, it is a marked improvement over the 600-day disparity with the United States, and the 488-day disparity with the European Union that Barua and Esmail (2013b) measured in the first year of analysis in 2005. [20]

As shown in figures 2a to 2g, in every year between 2012/13 and 2018/19, nearly every drug examined in this analysis was approved first in the United States or the European Union. In our sample of 224 drugs, we could identify only 13 cases over this time period where approval was given by Health Canada before it was approved in either the United States by the FDA or in the European Union by the EMA (or through the mutual recognition scheme). Further, there was only one drug in our sample that was approved in Canada, but not in either the United States or the European Union. Of the 218 drugs approved in both Canada and the United States, only 26 received approval in Canada first. Meanwhile, of the 205 drugs approved in both Canada and the European Union, 42 received approval in Canada first.

[20] Comparisons with the study made by Barua and Esmail (2013b) must be made with caution as the current study does not include vaccines in its analysis.

Table 1a: Median number of days drugs were approved in the United States before they were approved in Canada, by therapeutic class, 2012/13–2018/19

Anatomical Therapeutic Chemical (ATC) Category	Days	Number of drugs
Systemic hormonal preparations, excl. sex hormones and insulins	775	2
Genito-urinary system and sex hormones	655	6
Sensory organs	625	10
Alimentary tract and metabolism	524	36
Nervous system	501	16
Cardiovascular system	336	10
Various	280	6
Antineoplastic and immunomodulating agents	271	72
Dermatologicals	247	5
Musculo-skeletal system	232	3
Respiratory system	119	11
Blood and blood forming organs	40	20
Anti-infectives for systemic use	22	21

Table 1b: Median number of days drugs were approved in the European Union before they were approved in Canada, by therapeutic class, 2012/13–2018/19

Anatomical Therapeutic Chemical (ATC) Category	Days	Number of drugs
Sensory organs	780	5
Systemic hormonal preparations, excl. sex hormones and insulins	613	1
Genito-urinary system and sex hormones	541	6
Various	520.5	6
Alimentary tract and metabolism	447	35
Musculo-skeletal system	356	3
Nervous system	339	12
Blood and blood forming organs	118.5	20
Antineoplastic and immunomodulating agents	116	69
Respiratory system	105	13
Dermatologicals	68	4
Cardiovascular system	56	10
Anti-infectives for systemic use	54	21

Figure 2a: International differences in regulatory approval for drugs approved in Canada, **2012/13**

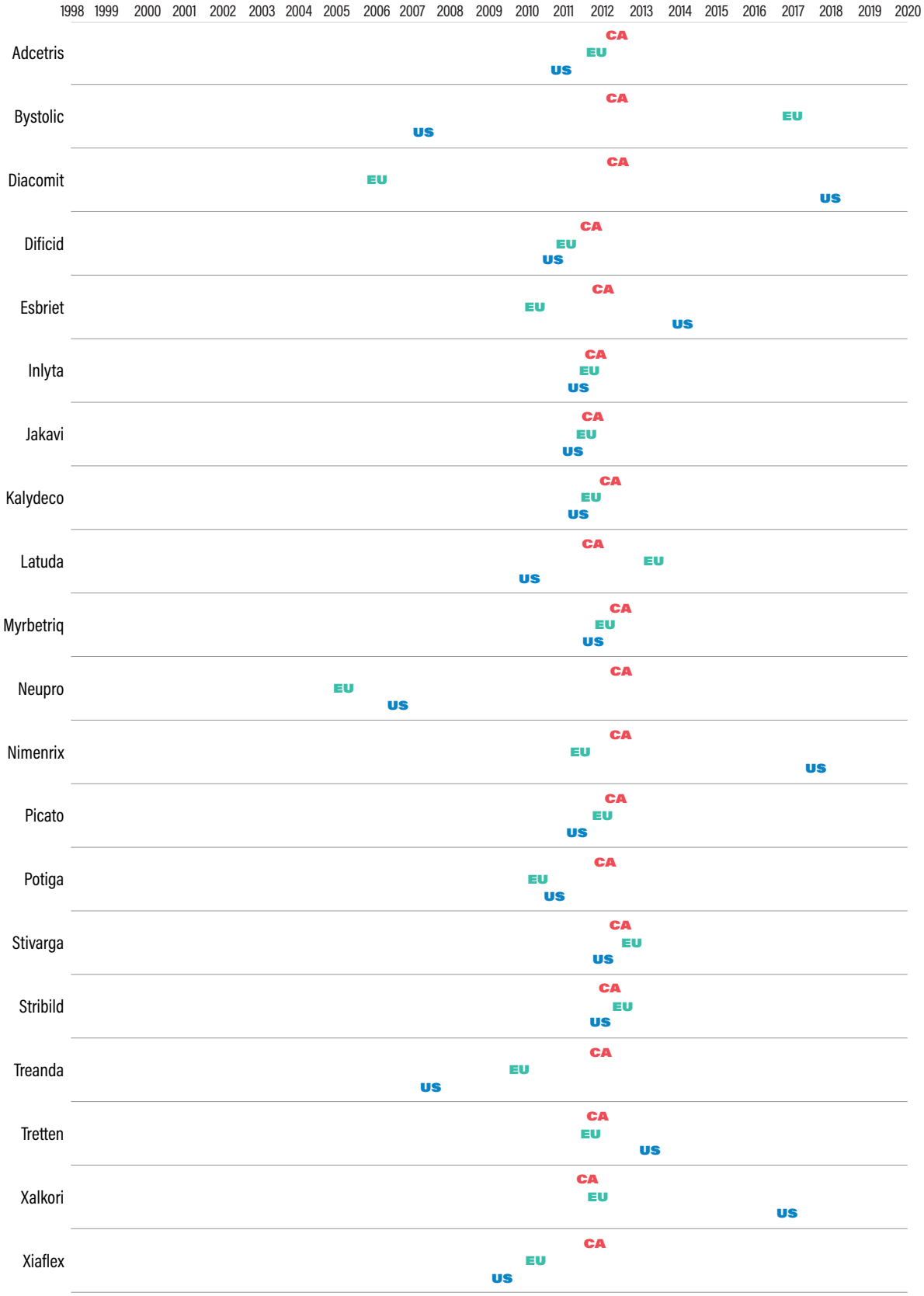


Figure 2b: International differences in regulatory approval for drugs approved in Canada, **2013/14**

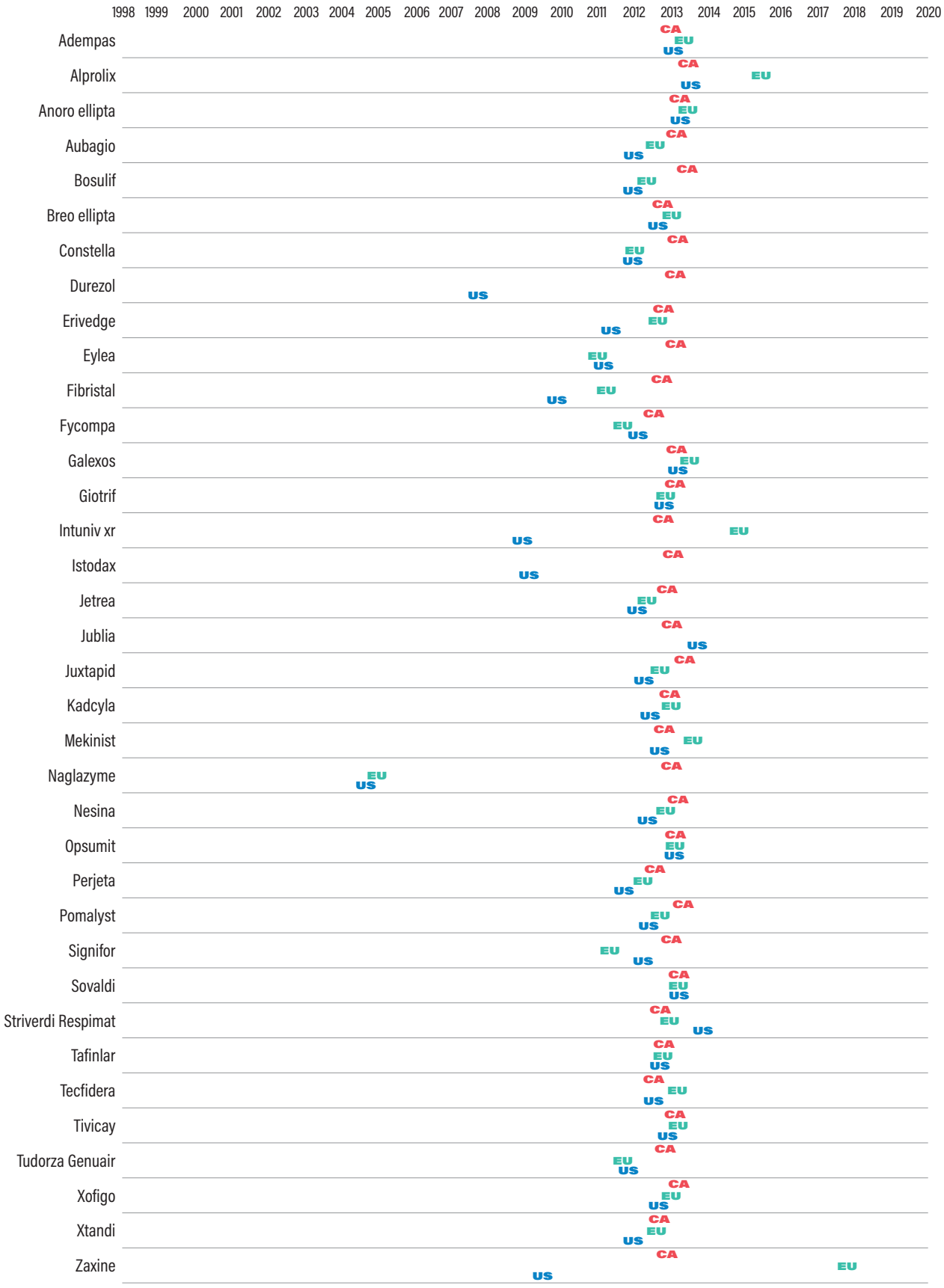


Figure 2c: International differences in regulatory approval for drugs approved in Canada, **2014/15**

Figure 2d: International differences in regulatory approval for drugs approved in Canada, **2015/16**

Figure 2e: International differences in regulatory approval for drugs approved in Canada, **2016/17**

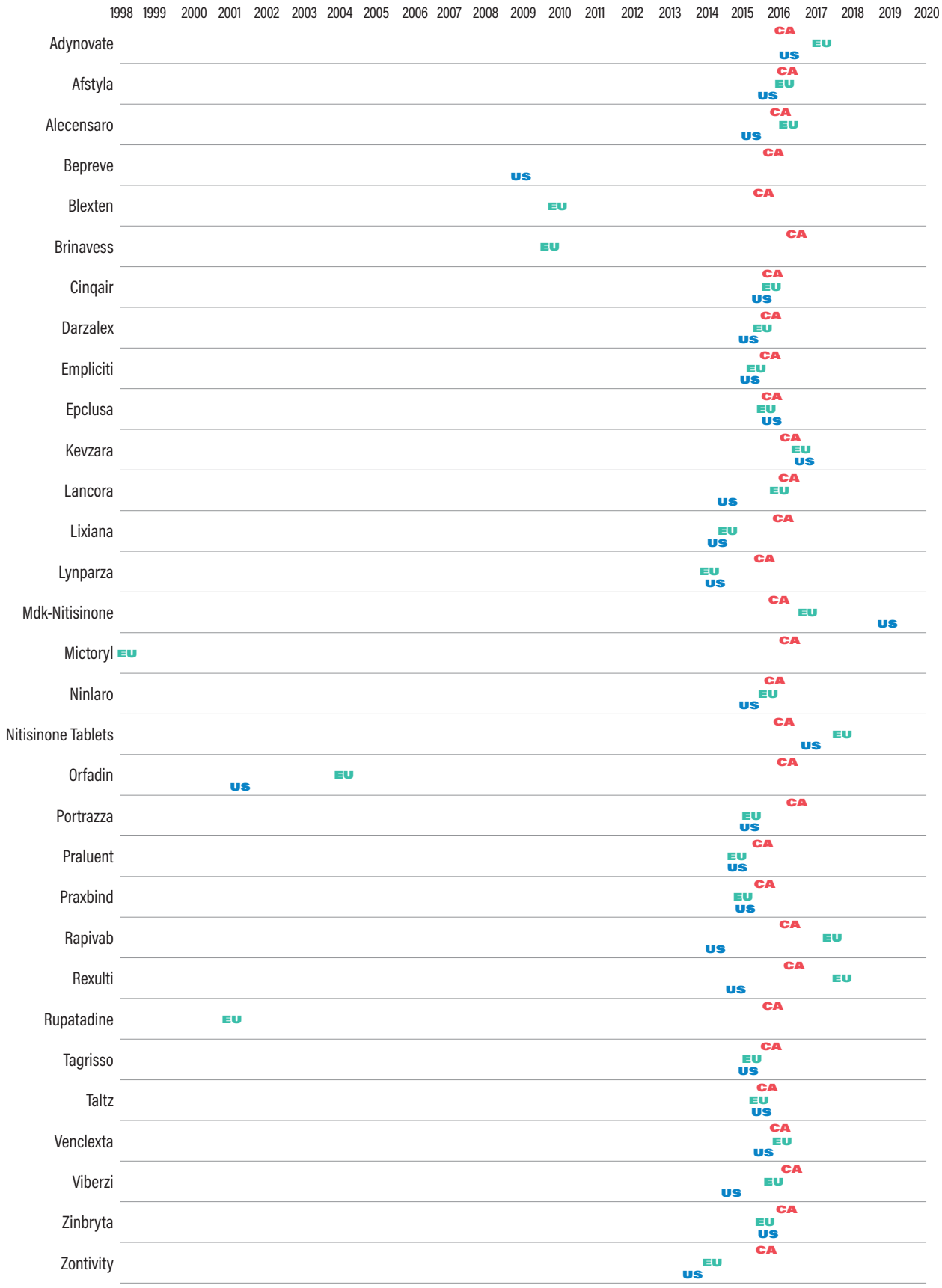


Figure 2f: International differences in regulatory approval for drugs approved in Canada, **2017/18**

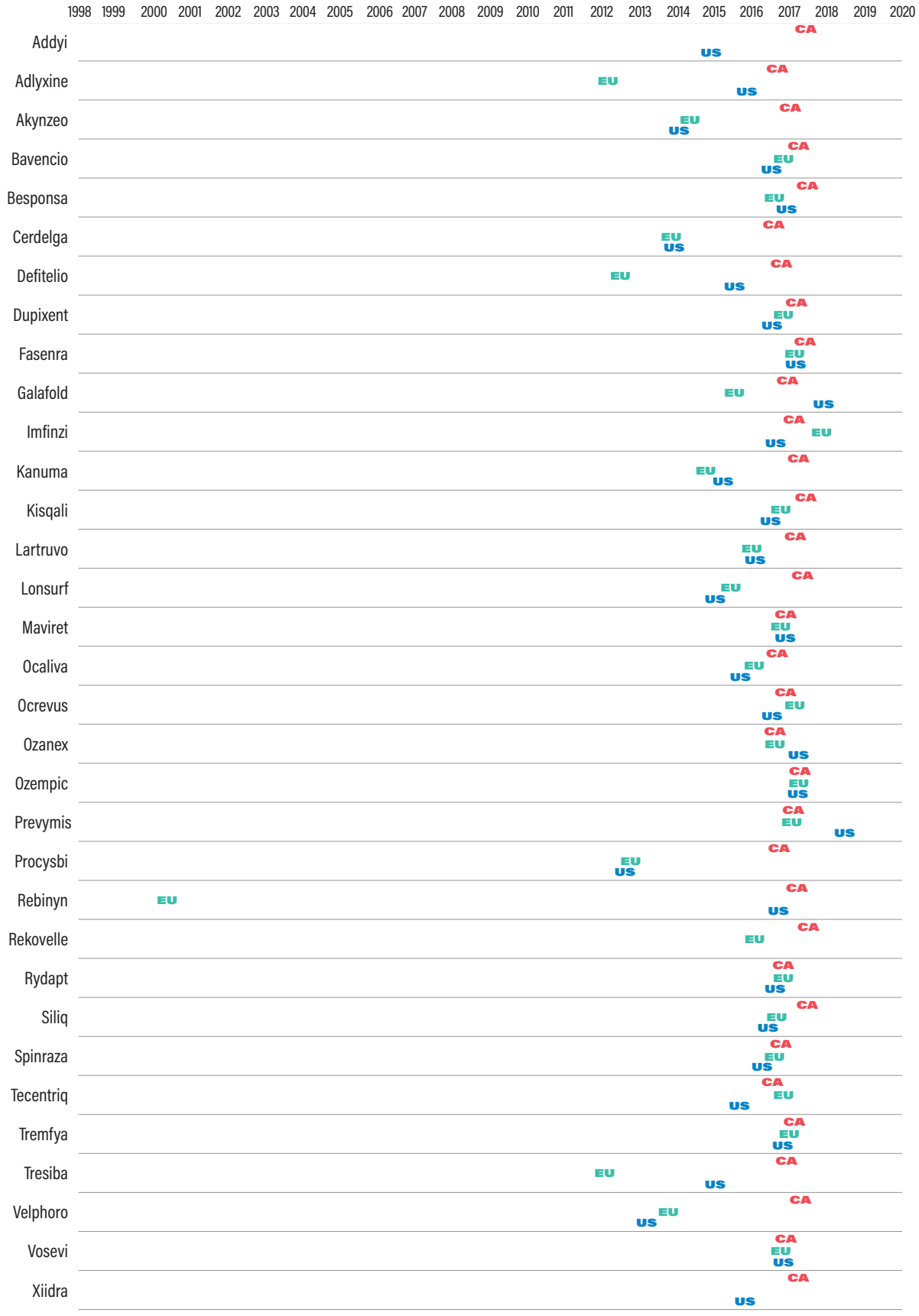


Figure 2g: International differences in regulatory approval for drugs approved in Canada, **2018/19**

Discussion

Dates of submission versus efficiency

The results above clearly indicate that Canadian patients suffer significantly delayed access to new, innovative medicines compared to their counterparts in the United States and the European Union. Some of this delay may be a result of differences in efficiency (Barua and Esmail, 2013a; Downing *et al.*, 2012; Rawson, 2012, 2018a). However, the more important factor is the presence of differences in the dates on which manufacturers submit new drugs to agencies for regulatory approval.

If we constrain our analysis to compare drugs for which submission dates are available, [21] the average [22] 468-day (285-day median) difference between approval dates in Canada and the United States (for 215 drugs) consists of an average 464-day (170-day median) difference between submission dates, and an average 4-day (38-day median) difference in efficiency. Similarly, the average 404-day (145-day median) difference between approval dates in Canada and the European Union (for 191 drugs) consists of an average 395-day (123-day median) difference between submission dates, and an average 9-day (−9 day median) difference in efficiency (figure 3).

Several reasons for this difference in dates of submission may exist, including differences in the market's attractiveness for investment in the face of the prevalent regime of intellectual-property protection, the size and sophistication of the potential market of consumers, regulatory controls on drug pricing, and the reimbursement policies practiced by public and private insurers. Another reason, more directly related to regulatory activities, is the extra financial burden incurred through user fees and the costs associated with creating a submission for a particular agency. Relevant considerations for Canada include the fact that the Canadian population and, thus, the market in Canada, is a fraction of the size of markets in the United States and the European Union. Further, the Canadian market is characterized by both long delays

[21] In the European Union, these largely exclude drugs approved through the mutual recognition procedure, while in the United States these would largely encompass biologics in Barua and Esmail, 2013. Given that biologics are usually approved quicker than therapeutics, the FDA may appear less efficient than it actually is in the analysis found in Barua and Esmail, 2013. In order to maintain international comparability, we use date of receipt by the FDA whenever available (the date of submission when date of receipt is unavailable).

[22] When examining individual components of delay for subsequent aggregation, it is more appropriate to compare averages than medians. This is because the sum of the medians of individual components will not necessarily add up to the total median difference (in approval dates) while it will for averages.

for coverage by provincial drug plans and a high rate of refusal to cover, as well as relatively weaker protections for intellectual property (Rovere and Skinner, 2012; Esmail, 2013; Lybecker, 2017). Any of these may provide incentives to delay or forego submission to Health Canada altogether.

While evidence on the relative importance of each of these factors is not available, several studies have shown that a number of drugs are not approved by Health Canada or possibly not submitted for approval in the first place. For example, the analysis by Downing and colleagues (2012) of 289 unique novel therapeutics approved by the FDA, EMA, and Health Canada identified 190 drugs approved by the FDA and the EMA but not Health Canada.

Incentives, duplication, and the potential for harm

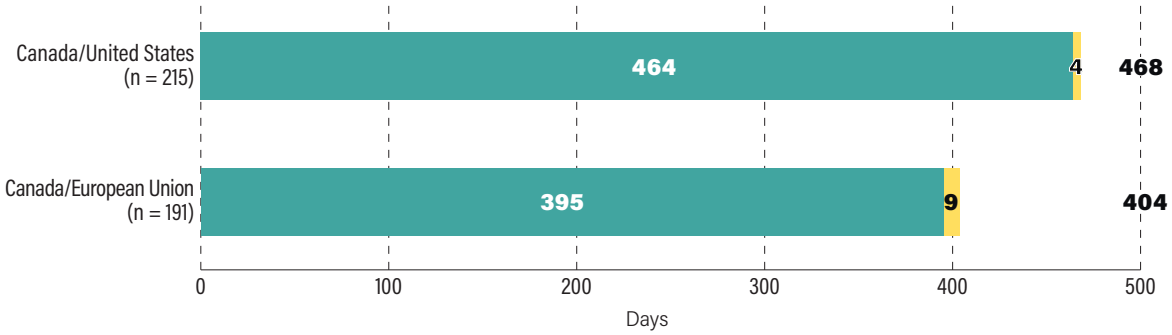
Health Canada is faced with the necessarily onerous task of striking "a balance between the potential health benefits and risks posed by all drugs and health products" (Health Canada, 2013b). Within this task, the agency is faced with the risk of making two types of mistakes, known as Type-I and Type-II errors (Graham, 2005). Type-I errors occur when regulators at Health Canada approve products that are later pulled from distribution because there are extensive negative consequences. Type-II errors occur if regulators at Health Canada deny approval for a medicine that would have had net beneficial effects for Canadians' health and well-being.

The negative effects of Type-I errors are far easier to measure, though evidence suggests that in such cases it is usually the drug manufacturers themselves who voluntarily withdraw the drug from the market rather than regulators forcing such withdrawal. For example, *Thelin* [23] (approved by Health Canada in 2007) was voluntarily pulled from the Canadian market by Pfizer following concerns about liver injury, even though no cases of liver failure associated with the drug had been reported in Canada (CBC, 2010). Further, even in cases where Health Canada has urged withdrawal, it has often been in response to actions initially taken outside the country (for additional examples, see Graham, 2005). For example, *Prexige* (approved by Health Canada in 2006) was withdrawn from the market at the request of Health Canada after it was pulled from the Australian market following reports of serious adverse effects on the liver in some patients (CBC, 2007a, 2007b). [24] Further, the benefits of agreements to recognize approvals by comparable

[23] This is also known as *Sitaxsentan*.

[24] There is also the matter of drugs being pulled from the market as a result of a perception of unacceptable risk of harm, when some patients would have made different risk/benefit trade-offs (in a fully informed sense) to gain the important positive effects of the medicine. *Vioxx* and *Prepulsid* may serve

Figure 3: Average difference (days) in submission and efficiency in the United States and the European Union compared to Canada, 2012/13–2018/19



Note: Totals may not add up as a result of rounding.

international agencies can be combined with the benefits of similar agreements that would recognize advisories, denials, and withdrawals. For example, a recent study by Perry and colleagues (2020) documenting safety advisories issued by regulatory agencies during a 10-year period found that the United Kingdom (469) and FDA (382) issued more advisories during this period than Health Canada (370).

The effects of Type-II errors are much harder to measure. Critically, these drugs do not appear on the market, rendering it impossible to judge the foregone benefits that would have accrued to Canadians. For example, it is not easily possible to quantify the number of Canadian lives lost because a particular new drug was not available in Canada.

Given the easily accessible and public nature of knowledge of the first but not the second type of error, regulators have a much larger incentive to avoid committing the Type-I errors at the expense of attention to Type-II. While this incentive is inherent in governmental regulatory approvals, the increasing complexity of products being approved may serve to increase the possibility of Type-II errors being made by risk-averse government regulators. While this increasing incentive is real, we may never know how many benefits have been lost as a result of the difficulty in measuring such errors.

One way to minimize the loss of potential benefits, at least for Canadians, would be to recognize that the approach taken by Health Canada is largely unnecessary. The data

as good examples of this (Graham, 2005). Importantly, all drugs have risks associated with them, and there is an important question here about who is best placed to judge the risk/benefit trade-off, and whether a centralized judgment by regulators is appropriate in all cases for individual patients with varying tolerances of ill-effects and illness, and with varying sensitivities to risk. The ability of regulators to identify possible risks correctly in the first place is itself also drawn into question because some serious side effects do not become apparent until after a drug has been approved. This is in part because clinical trials are limited in the numbers of patients involved and their health and genetic profiles.

shown above demonstrate clearly that Health Canada not only approves medicines slower than its European and American counterparts after submission, but that submission of medicines for approval in Canada typically comes many months if not more than a year later than in the United States or the European Union (not counting those medicines never submitted for approval). Yet Health Canada's approval process largely duplicates what is already being done (earlier and sometimes more efficiently) in the United States and the European Union, which means the benefits of this process for Canadians are limited at best. [25]

Critically, Health Canada's approach to scientific review of new drugs is not considerably different from those in the United States and the European Union (Rawson, 2013; Rawson, 2003; Paul, 2001). Canadian laws and regulations regarding prescription drugs have generally followed those of the United States (Graham, 2005). Further, there are many similarities among the drug-approval processes in Canada, the United States, and the European Union: Paul (2001) notes that the FDA's "procedures and requirements are the framework for those of the EU and Canada" (2001: 233).

All of this means that Canadians are denied the health benefits of many medicines for months, if not years, waiting for their government to duplicate approvals already provided in other jurisdictions. In addition, Canadians, possibly as a result of the costs of entering a small and highly regulated market, receive access to fewer medicines in total than their counterparts in other developed nations, leaving them with fewer therapeutic options and the possibility of worse health outcomes. And, in addition to these foregone benefits lie the costs to taxpayers and drug manufacturers of funding this duplicative process.

The question then must be: why duplicate the processes of the FDA and the EMA in Canada? Both agencies are highly respected organizations with excellent resources that ostensibly maintain standards of scientific rigour in their approvals that are similar to those maintained by Health Canada. Further, the risk of error for them is (in raw numbers) substantially larger than the risk of error at Health Canada, considering that they are approving access to medicines for populations that are roughly 10 to 15 times the size of the Canadian population. Unless we are to believe that Health Canada provides regulatory reviews that are far superior to those provided by the FDA and the EMA, or that Health Canada undertakes examinations not undertaken by its American and European counterparts, there is little reasonable argument for duplicating their processes while forcing Canadians to wait for access to health-improving medicines.

[25] Critically, there is no reason to believe that the drug-approval process is not subject to the reality of decreasing marginal returns (there is less benefit as more of an activity takes place).

Rawson (2013) examined safety warnings for 454 medicines approved in Canada and the United States between 1992 and 2011. He found that 3.4% of drugs were discontinued for safety reasons in the United States compared to 3.1% in Canada. Of the 454 drugs examined, 158 drugs (34.8%) had at least one black-box warning or were discontinued in the United States compared to 43.8 % of drugs in Canada that were either discontinued or had warnings in Canada's Product Monograph or the MedEffect database, though the list of drugs that received warnings did not match in the two countries. While this latter statistic might suggest greater rigour at Health Canada, further investigation suggests this may not be the case. As noted above, Health Canada's apparently higher rate of issuing safety warnings may be indicative of a greater aversion to risk and regulatory caution, particularly when presented with complex drugs that provide novel benefits but have unfamiliar risks. Further, it must be noted that in the past Health Canada has lagged the FDA in issuing warnings, and there remains the important matter of the large number of drugs approved in the United States that are yet to be or will ultimately not be approved in Canada and the consequent foregone health benefits (Graham, 2005). [26]

It is this latter point that is most critical in this discussion. As noted above, by far the greatest part of the delay before new drugs are available to Canadians is the delay in submission to Health Canada, which is outside of the agency's control. Given the low and similar rate of withdrawal of drugs (at least, by the FDA and Health Canada), it can be said that this delay is denying Canadians access to many medicines that will ultimately be found sufficiently safe and effective not to be withdrawn from the marketplace. This provides a strong reason to consider seriously whether or not Health Canada's mandatory approval process is in fact beneficial to Canadians.

Indeed, keeping in mind Canada's relatively small population and limited market, there is great value in considering whether Health Canada's mandatory approvals should be replaced with agreements to recognize drug approvals by comparable international agencies. Under such an approach, approval by the FDA or EMA could be considered sufficient warrant for market access in Canada. [27] The clear benefits of such an

[26] An analysis of the appendices in Rawson (2013) shows that 93.8% of drugs approved in Canada were also approved in the United States between 1992 and 2011 (not including drugs approved in the United States prior to 1992), while 81.9% of drugs approved in the United States were also approved in Canada. Importantly, the rate of drugs approved only in the United States increased over time, reaching 36.8% in the period from 2007 to 2011; this may be because drugs that have been submitted and approved in the United States are yet to be submitted or are under review in Canada.

[27] We very specifically note FDA or EMA here to minimize delay for Canadians. There is little obvious reason to believe (and little research to suggest) that either the FDA or EMA provides a superior regulatory review relative to the other. Further, the FDA and EMA do not always agree on drug approvals,

approach would be a reduction in the costs of entry to the Canadian marketplace and a significant reduction in the delay Canadians endure before new drugs are available to them. Of course, this does not change the incentive to prefer Type-I errors over Type-II errors at the FDA and EMA, but it does reduce the risk of compounding such errors at Health Canada.

This is not to say that Canadians must rely on reviews of drug safety from other jurisdictions, or that Health Canada should be deprived the right to review drugs or ban drugs from the Canadian marketplace. This process can be implemented while maintaining Health Canada's authority to provide safety warnings and to require withdrawal of a drug from the Canadian marketplace, and while maintaining Health Canada's approval process on a non-mandatory basis. Specifically, while FDA and EMA approvals could readily be accepted as sufficient for market entry, they could also be subject to a labeling requirement stating the approval was through the FDA and EMA and that Health Canada had not yet approved that particular medicine. This could give Canadians and their health-care providers the opportunity to decide for themselves if they felt Health Canada's approval process provided additional safety or protection from the risks associated with a new drug in addition to the processes undertaken in either the United States or the European Union. Thus, earlier access would be facilitated for Canadian patients willing to take on the possibility of a higher level of risk for the potential benefit of earlier relief, while more risk-averse patients would be able to wait for Canada-specific approval voluntarily.

A new role for Health Canada

Establishing agreements to recognize approvals by comparable international agencies could free up considerable resources at Health Canada. While there is merit in doing so, these resources need not be saved in their entirety. There are two important tasks, both of which are possibly under-resourced in Canada at present, that might be undertaken instead.

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which may be the result of differences in risk perception, differences in perceived patient needs, or differences in the Type-I and Type-II errors each makes. Considering the benefits of access to medicines highlighted earlier in this paper, and the fact that both the FDA and EMA can be considered reputable agencies, the argument for preferring one or the other or requiring a similar decision from both for recognition seems weak. However, there is the possibility that a more complex decision rule could be enforced in Canada where both FDA and EMA approval are required and where a third regulatory agency's decision could be employed in cases of disagreement. It must be recognized, however, that any such rule would increase the delay in access to new drugs for Canadians in comparison to our simple rule, though it would still (depending on the third agency chosen) likely result in earlier access than the present duplicative regime.

There is increasing demand for more active surveillance (or "pharmacovigilance") of drug safety and risk after approvals have been granted by regulatory agencies. Importantly, because of the limitations of clinical trials, some serious side effects do not become apparent until after a drug has been approved and is in broad use. While some positive steps have already been taken in this area in Canada, for example by the establishment of the Drug Safety and Effectiveness Network (DSEN), most post-market drug-surveillance systems depend on voluntary reporting of adverse drug reactions (ADRs). These largely *passive* systems capture only between 1% and 10% of adverse drug reactions and fall well short of active approaches that would involve efforts to scrutinize interlinked drug and health-care databases for ADRs on an ongoing basis (Wiktorowicz, 2010). Of course, the latter is a costly and intensive process requiring researchers to seek out potential problems, create risk-management plans and research trials, create registries to track information, and ultimately make recommendations on complex risk/benefit trade-offs. In reducing duplicative efforts, Health Canada's resources might be better deployed in this area either directly or by creating incentives for optimal reporting of ADRs.

Another option would be funding and supporting better communication of the risks associated with certain drugs so that physicians and patients can make more informed decisions about their use of drugs and about the risk/benefit trade-off they are facing when choosing a particular treatment option. This is particularly important when increasingly complex products are being approved. Importantly, this leaves more control of the risk/benefit trade-off in the hands of those directly exposed to it rather than to risk-averse regulators who have strong incentives to minimize risk at the expense of lost benefit.

Indeed, this may be an ideal opportunity for Health Canada to shift away from performing a largely unnecessary function that may be subject to negative marginal returns, and towards one whose importance is being increasingly identified.

Conclusion

At present, not only are patients in Canada being denied access to new pharmaceutical therapies in a timely manner, but valuable resources are being funneled into a process that is arguably redundant. In addition, the delayed approval of new pharmaceuticals highlighted in this study are particularly concerning at a time when Canada's federal government is considering the introduction of restrictive price controls on new pharmaceuticals. To the extent that restrictive price controls may have contributed in the past to Canadians having delayed access to innovative pharmaceuticals in comparison to the those living in the United States and the European Union, it is likely that the new regulations of the Patented Medicines Pricing Board set to come into effect on July 1, 2021 will further exacerbate such delays (Acri, 2018; Rawson, 2018b; Globerman and Barua, 2019).

While the potential for harm that accompanies any new medicine on the market may provide some justification for regulatory approval in general, the requirement that such approval be duplicated in one jurisdiction after having already been received in another with comparable standards is less justifiable. Instead of duplicating the activities of other agencies, it makes more sense to rely on their expertise by accepting US or European regulatory approvals as sufficient for market access in Canada. This would speed access to new drugs in Canada (and reduce the costs of compliance with Canadian regulations) while maintaining a strict regime for drug approvals undertaken by well-resourced agencies.

If Canada had recognition agreements with the European Union and the United States (accepting approval from either body as equivalent), patients could have received access to 223 new pharmaceutical therapies (of the 224 in our sample) a median 383 (average 742) days earlier. Patients would also likely have received access to many drugs approved by the EMA or FDA but not available in Canada because they were either not approved by Health Canada or were simply not submitted for marketing approval in Canada at all.

While there is a case for the resources currently devoted to Health Canada's duplicative approvals process to be simply saved, these resources might, on the other hand, be put towards activities that are not well supported at present. Importantly, some could be put towards post-market surveillance activities and be used to improve the quality of information about the risk/benefit trade-off of various medicines for Canadians.

The result of such recognition agreements would be faster access to the health and social benefits created by new drugs, paired with a higher level of information about the potential risk/benefit trade-offs associated with each for Canadian patients and physicians.

Appendix A: Drugs Approved in Canada, 2012/13–2018/19, Included in Analysis, with EMA and FDA Equivalents

Medicinal Ingredient	Canada	European Union	United States
Brigatinib	Alunbrig	Alunbrig	Alunbrig
Suvorexant	Belsomra		Belsomra
Bictegravir Sodium Emtricitabine Tenofovir Alafenamide Hemifumarate	Biktarvy	Biktarvy	Biktarvy
Cabozantinib	Cabometyx	Cometriq	Cometriq
Isavuconazonium Sulfate	Cresemba	Cresemba	Cresemba
Decitabine	Demylocan	Dacogen	Dacogen
Apalutamide	Erleada	Erleada	Erleada
Crisaborole	Eucrisa	Staquis	Eucrisa
Pralatrexate	Folotyn		Folotyn
Enasidenib	Idhifa		Idhifa
Lorlatinib	Lorbrena	Lorviqua	Lorbrena
Iron Isomaltoside 1000	Monoferric	Monofer	Monoferric
Baricitinib	Olumiant	Olumiant	Olumiant
Safinamide	Onstryv	Xadago	Xadago
Elagolix Sodium	Orilissa		Orilissa
Doravirine	Pifeltro	Pifeltro	Pifeltro
Edaravone	Radicava		Radicava
Calcifediol	Rayaldee	Calcifediol	Rayaldee
Ertugliflozin	Steglatro	Steglatro	Steglatro
Tezacaftor Ivacaftor	Symdeko	Symkevi	Symdeko
Inotersen Sodium	Tegsedi	Tegsedi	Tegsedi
Patiromer Sorbitex Calcium	Veltassa	Veltassa	Veltassa
Dacomitinib	Vizimpro	Vizimpro	Vizimpro
Latanoprostene Bunod	Vyzulta		Vyzulta
Telotristat Etiprate	Xermelo	Xermelo	Xermelo
Dalbavancin	Xydalba	Xydalba	Dalvance
Erenumab	Aimovig	Aimovig	Aimovig

Medicinal Ingredient	Canada	European Union	United States
Cerliponase Alfa	Brineura	Brineura	Brineura
Burosumab	Crysvita	Crysvita	Crysvita
Emicizumab	Hemlibra	Hemlibra	Hemlibra
Antihemophilic Factor (Recombinant B-Domain Deleted PEGylated)	Jivi	Jivi	Jivi
Tisagenlecleucel	Kymriah	Kymriah	Kymriah
Lutetium (177Lu) Oxodotreotide	Lutathera	Lutathera	Lutathera
Cenegermin	Oxervate	Oxervate	Oxervate
Lanadelumab	Takhzyro	Takhzyro	Takhzyro
Dinutuximab	Unituxin	Unituxin	Unituxin
Von Willebrand Factor (Recombinant)	Vonvendi	Veyvondi	Vonvendi
Axicabtagene Ciloleucel	Yescarta	Yescarta	Yescarta
Flibanserin	Addyi		Addyi
Lixisenatide	Adlyxine	Lyxumia	Adlyxin
Netupitant Palonosetron as Palonosetron Hydrochloride	Akynzeo	Akynzeo	Akynzeo
Eliglustat as Eliglustat Tartrate	Cerdelga	Cerdelga	Cerdelga
Migalastat as Migalastat Hydrochloride	Galafold	Galafold	Galafold
Ribociclib as Ribiciclib Succinate	Kisqali	Kisqali	Kisqali
Trifluridine Tipiracil Hydrochloride	Lonsurf	Lonsurf	Lonsurf
Pibrentasvir Glecaprevir	Maviret	Maviret	Mavyret
Obeticholic Acid	Ocaliva	Ocaliva	Ocaliva
Ozenoxacin	Ozanex	Ozanex	Xepi
Letermovir	Prevymis	Prevymis	Prevymis
Cysteamine as Cysteamine Bitartrate	Procysbi	Procysbi	Procysbi
Midostaurin	Rydapt	Rydapt	Rydapt
Nusinersen as Nusinersen Sodium	Spinraza	Spinraza	Spinraza
Sucroferric Oxyhydroxide	Velphoro	Velphoro	Velphoro
Sofosbuvir Velpatasvir Voxilaprevir	Vosevi	Vosevi	Vosevi
Lifitegrast	Xiidra		Xiidra
Avelumab	Bavencio	Bavencio	Bavencio
Inotuzumab Ozogamicin	Besponsa	Besponsa	Besponsa
Defibrotide	Defitelio	Defitelio	Defitelio
Dupilumab	Dupixent	Dupixent	Dupixent
Benralizumab	Fasenra	Fasenra	Fasenra
Durvalumab	Imfinzi	Imfinzi	Imfinzi

Medicinal Ingredient	Canada	European Union	United States
Sebelipase Alfa	Kanuma	Kanuma	Kanuma
Olaratumab	Lartruvo	Lartruvo	Lartruvo
Ocrelizumab	Ocrevus	Ocrevus	Ocrevus
Semaglutide	Ozempic	Ozempic	Ozempic
Follitropin Delta	Rekovelle	Rekovelle	
Coagulation Factor IX (Recombinant) pegylated	Rebinyn	Nonafact	Rebinyn
Brodalumab	Siliq	Kyntheum	Siliq
Atezolizumab	Tecentriq	Tecentriq	Tecentriq
Guselkumab	Tremfya	Tremfya	Tremfya
FLEXTOUCH Insuline Degludec	Tresiba	Tresiba	Tresiba
Alectinib as Alectinib Hydrochloride	Alecensaro	Alecensa	Alecensa
Bepotastine Besilate	Bepreve		Bepreve
Bilastine	Blexten	Bitosen	
Vernakalant Hydrochloride	Brinavess	Brinavess	
Sofosbuvir Velpatasvir	Epclusa	Epclusa	Epclusa
Ivabradine as Ivabradine Hydrochloride	Lancora	Ivabradine Zentiva	Corlanor
Edoxaban	Lixiana	Lixiana	Savaysa
Olaparib	Lynparza	Lynparza	Lynparza
Nitisinone	Mdk-Nitisinone	Nitisinone Mdk	Nitisinone
Propiverine Hydrochloride	Mictoryl	Detrunorm	
Ixazomib as Ixazomib Citrate	Ninlaro	Ninlaro	Ninlaro
Nitisinone	Nitisinone tablets	Nityr	Nityr (Nitisinone) tablets
Nitisinone	Orfadin	Orfadin	Orfadin
Peramivir	Rapivab	Alpivab	Rapivab
Brexpiprazole	Rexulti	Rxulti	Rexulti
Rupatadine as Rupatadine Fumarate	Rupatadine	Rupafin	
Osimertinib as Osimertinib Mesylate	Tagrisso	Tagrisso	Tagrisso
Venetoclax	Venclexta	Venclyxto	Venclexta
Eluxadoline	Viberzi	Truberzi	Viberzi
Vorapaxar Sulfate	Zontivity	Zontivity	Zontivity
Antihemophilic Factor (Recombinant) PEGylated	Adynovate	Adynovi	Adynovate
Lonoctocog Alfa	Afstyla	Afstyla	Afstyla
Reslizumab	Cinqair	Cinqaero	Cinqair
Daratumumab	Darzalex	Darzalex	Darzalex
Elotuzumab	Empliciti	Empliciti	Empliciti

Medicinal Ingredient	Canada	European Union	United States
Sarilumab	Kevzara	Kevzara	Kevzara
Necitumumab	Portrazza	Portrazza	Portrazza
Alirocumab	Praluent	Praluent	Praluent
Idarucizumab	Praxbind	Praxbind	Praxbind
Ixekizumab	Taltz	Taltz	Taltz
Daclizumab Beta	Zinbryta	Zinbryta	Zinbryta
Lubiprostone	Amitiza	Amitiza	Amitiza
Sugammadex	Bridion	Bridion	Bridion
Brivaracetam	Brivlera	Briviact	Briviact
Carglumic Acid	Carbaglu	Carbaglu	Carbaglu
Cobimetinib Fumarate	Cotellic	Cotellic	Cotellic
Daclatasvir	Daklinza	Daklinza	Daklinza
Sacubitril Valsartan	Entresto	Entresto	Entresto
Levomilnacipran Hydrochloride	Fetzima		Fetzima
Elvitegravir Cobicistat Emtricitabine Tenofovir Alafenamide Hemifumarate	Genvoya	Genvoya	Genvoya
Palbociclib	Ibrance	Ibrance	Ibrance
Ponatinib Hydrochloride	Iclusig	Iclusig	Iclusig
Empagliflozin	Jardiance	Jardiance	Jardiance
Carfilzomib	Kyprolis	Kyprolis	Kyprolis
Lenvatinib Mesylate	Lenvima	Lenvima	Lenvima
Mifepristone and Misoprostol	Mifegymiso	Mifegyne	Mifeprex
Naloxegol Oxalate	Movantik	Moventig	Movantik
Nintedanib Esilate	Ofev	Ofev	Ofev
Ivacaftor Lumacaftor	Orkambi	Orkambi	Orkambi
Glycerol Phenylbutyrate	Ravicti	Ravicti	Ravicti
Asunaprevir	Sunvepra		
Selexipag	Uptravi	Uptravi	Uptravi
Polidocanol	Varithena		Varithena
Vilazodone Hydrochloride	Viibryd		Viibryd
Finafloxacin	Xtoro		Xtoro
Elbasvir Grazoprevir	Zepatier	Zepatier	Zepatier
Ceftolozane Sulfate and Tazobactam Sodium	Zerbaxa	Zerbaxa	Zerbaxa
Blinatumomab	Blincyto	Blincyto	Blincyto
Ramucirumab	Cyramza	Cyramza	Cyramza

Medicinal Ingredient	Canada	European Union	United States
Albiglutide	Eperzan	Eperzan	Tanzeum
Albutrepenonacog Alfa	Idelvion	Idelvion	Idelvion
Pembrolizumab	Keytruda	Keytruda	Keytruda
Mepolizumab	Nucala	Nucala	Nucala
Antihemophilic Factor (Recombinant) Porcine Sequence	Obizur	Obizur	Obizur
Nivolumab	Opdivo	Opdivo	Opdivo
Peginterferon Beta-1A	Plegridy	Plegridy	Plegridy
Evolocumab	Repatha	Repatha	Repatha
Teduglutide	Revestive	Revestive	Gattex
Asfotase Alfa	Strensiq	Strensiq	Strensiq
Dulaglutide	Trulicity	Trulicity	Trulicity
Eslicarbazepine Acetate	Aptiom	Zebinix	Aptiom
Conjugated Estrogens and Bazedoxifene Acetate	Duavive	Duavive	Duavee
Azelastine Hydrochloride and Fluticasone Propionate	Dymista	Dymista Nasenspray	Dymista
Tesamorelin Acetate	Egrifta		Egrifta
Icatibant Acetate	Firazyr	Firazyr	Firazyr
Dapagliflozin	Forxiga	Forxiga	Farxiga
Ledipasvir and Sofosbuvir	Harvoni	Harvoni	Harvoni
Ritonavir Paritaprevir Ombitasvir Dasabuvir	Holkira Pak	Viekirax	Viekira Xr
Ibrutinib	Imbruvica	Imbruvica	Imbruvica
Canagliflozin	Invokana	Invokana	Invokana
Apremilast	Otezla	Otezla	Otezla
Sodium Phenylbutyrate	Pheburane	Pheburane	Sodium Phenylbutyrat
Bromfenac Sodium Sesquihydrate	Prolensa	Yellox	Prolensa
Tafluprost	Saflutan	Taflotan	Zioptan
Tedizolid Phosphate	Sivextro	Sivextro	Sivextro
Vortioxetine Hydrobromide	Trintellix	Brintellix	Trintellix
Tofacitinib Citrate	Xeljanz	Xeljanz	Xeljanz
Idelalisib	Zydelig	Zydelig	Zydelig
Secukinumab	Cosentyx	Cosentyx	Cosentyx
Taliglucerase Alfa	Elelyso		Elelyso
Antihemophilic Factor (Recombinant BDD) FC Fusion Protein	Eloctate	Eloctate	Eloctate
Vedolizumab	Entyvio	Entyvio	Entyvio
Obinutuzumab	Gazyva	Gazyva	Gazyva

Medicinal Ingredient	Canada	European Union	United States
Simoctocog Alfa	Nuwiq	Nuwiq	Nuwiq
Siltuximab	Sylvant	Sylvant	Sylvant
Elosulfase Alfa	Vimizim	Vimizim	Vimizim
Turoctocog Alfa	Zonovate	Novoeight	Esperoct
Riociguat	Adempas	Adempas	Adempas
Umeclidinium Bromide and Vilanterol Trifenatate	Anoro Ellipta	Anoro Ellipta	Anoro Ellipta
Teriflunomide	Aubagio	Aubagio	Aubagio
Bosutinib	Bosulif	Bosulif	Bosulif
Fluticasone Furoate Vilanterol Trifenatate	Breo Ellipta	Relvar Ellipta	Breo Ellipta
Linaclotide	Constella	Constella	Linzess
Difluprednate	Durezol		Durezol
Vismodegib	Erivedge	Erivedge	Erivedge
Ulipristal Acetate	Fibristal	Esmya	Ella
Perampanel	Fycompa	Fycompa	Fycompa
Simeprevir	Galexos	Olysio	Olysio
Afatinib Dimaleate	Giotrif	Giotrif	Gilotrif
Guanfacine Hydrochloride	Intuniv Xr	Intuniv	Intuniv
Romidepsin	Istodax		Istodax
Efinaconazole	Jublia		Jublia
Lomitapide Mesylate	Juxtapid	Lojuxta	Juxtapid
Trametinib	Mekinist	Mekinist	Mekinist
Alogliptin Benzoate	Nesina	Vipidia	Nesina
Macitentan	Opsumit	Opsumit	Opsumit
Pomalidomide	Pomalyst	Pomalidomide Celgene	Pomalyst
Pasireotide	Signifor	Signifor	Signifor
Sofosbuvir	Sovaldi	Sovaldi	Sovaldi
Olodaterol Hydrochloride	Striverdi Respimat	Striverdi Respimat	Striverdi Respimat
Dabrafenib	Tafinlar	Tafinlar	Tafinlar
Dimethyl Fumarate	Tecfidera	Tecfidera	Tecfidera
Dolutegravir Sodium	Tivicay	Tivicay	Tivicay
Aclidinium Bromide	Tudorza Genuair	Bretaris Genuair	Tudorza Pressair
Enzalutamide	Xtandi	Xtandi	Xtandi
Rifaximin	Zaxine	Xifaxanta	Xifaxan
Recombinant Human Coagulation Factor IX FC Fusion Protein	Alprolix	Alprolix	Alprolix

Medicinal Ingredient	Canada	European Union	United States
Aflibercept	Eylea	Eylea	Eylea
Ocriplasmin	Jetrea	Jetrea	Jetrea
Trastuzumab Emtansine	Kadcyla	Kadcyla	Kadcyla
Galsulfase	Naglazyme	Naglazyme	Naglazyme
Pertuzumab	Perjeta	Perjeta	Perjeta
Radium-223 Dichloride Radium RA-223 Chloride	Xofigo	Xofigo	Xofigo
Nebivolol Hydrochloride	Bystolic	Nebivolol Aurobindo	Bystolic
Stiripentol	Diacomit	Diacomit	Diacomit
Fidaxomicin	Dificid	Dificlir	Dificid
Pirfenidone	Esbriet	Esbriet	Esbriet
Axitinib	Inlyta	Inlyta	Inlyta
Ruxolitinib Phosphate	Jakavi	Jakavi	Jakafi
Ivacaftor	Kalydeco	Kalydeco	Kalydeco
Lurasidone Hydrochloride	Latuda	Latuda	Latuda
Mirabegron	Myrbetriq	Betmiga	Myrbetriq
Rotigotine	Neupro	Neupro	Neupro
Ingenol Mebutate	Picato	Picato	Picato
Ezogabine	Potiga	Trobalt	Potiga
Regorafenib	Stivarga	Stivarga	Stivarga
Elvitegravir and Emtricitabine and Tenofovir Disoproxil Fumarate and Cobicistat	Stribild	Stribild	Stribild
Bendamustine Hydrochloride	Treanda	Levact	Treanda
Crizotinib	Xalkori	Xalkori	Xalkori
Brentuximab Vedotin	Adcetris	Adcetris	Adcetris
Meningococcal polysaccharide groups A C W-135 and Y conjugate vaccine Tetanus Toxoid	Nimenrix	Nimenrix	Menactra
Catridecacog	Tretten	Novothirteen	Tretten
Collagenase Clostridium Histolyticum	Xiaflex	Xiapex	Xiaflex

Appendix B: Drugs Approved in Canada 2012/13–2018/19, Excluded from Analysis

1 Diagnostic agents, contrast media, diagnostic radio pharmaceuticals and disinfectants

Note: Diagnostic agents and contrast media are excluded from our analysis as these might be considered non-therapeutic agents (see for example Downing et al., 2012).

a Dotarem
b Datscan
c Neuraceq

2 Drugs unable to be correctly matched, or missing key regulatory dates

a Panhematin
b Zaltrap
c Prochymal
d Rosiver

3 Immune Sera and Immunoglobulins

a Anthrasil
b BAT

4 Vaccines

a Biothrax
b Shingrix
c Trumenba
d Gardasil 9
e Bexsero
f Arepanrix H5N1
g Nimenrix

Note: *Firazyr* was designated an orphan drug by the EMA in 2003. However, we have used its 2008 CHMP approval in order to be conservative with our estimates.

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