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The Case for Mutual Recognition of Drug Approvals

by Bacchus Barua and Nadeem Esmail

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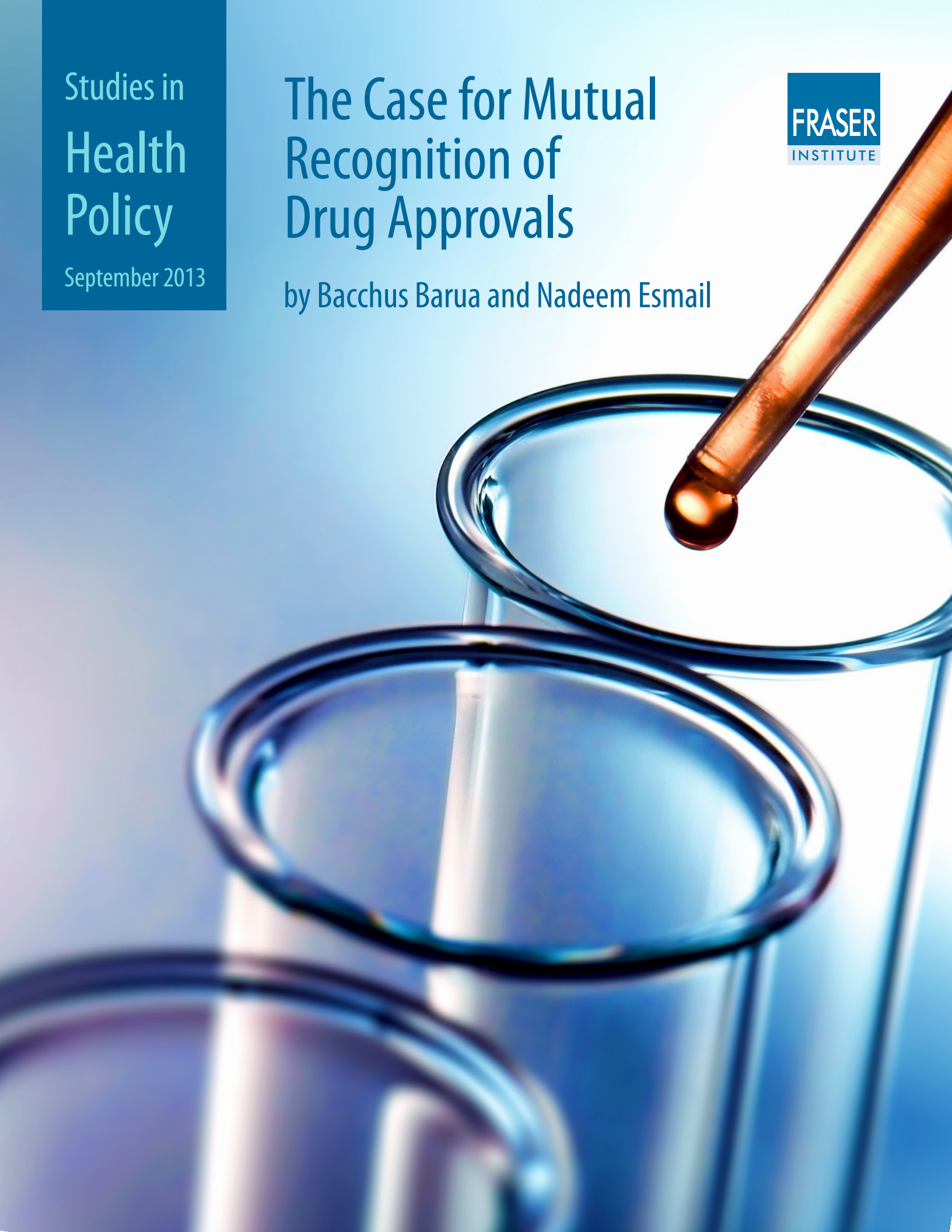

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Executive summary

Modern medicines improve both health outcomes and quality of life for those stricken with illness. Medicines available today 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.

However, in part because of governmental regulations and approvals, access to these newer (and superior) drugs is not equal across developed countries. Critically, new medicines are only accessible by 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).

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

Past studies have shown that Health Canada both takes longer to approve medicines, and approves fewer medicines than its American and European counterparts (Downing et al., 2012; Rawson, 2013; Barua and Esmail, 2013). However, these studies do not necessarily provide a true representation of differences regarding when drugs are eligible for sale in the three jurisdictions. Critically, a delay in accessing 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 better capture the delay in timely access to 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 centralized

approval procedure and the 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 access to new medicines in Canada in comparison with access in the United States and Europe.

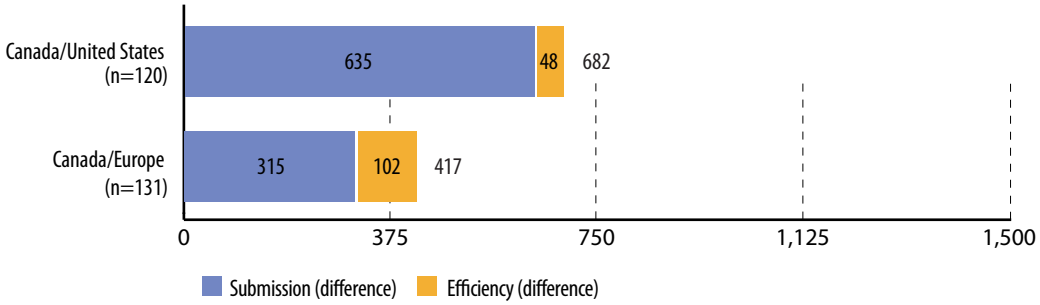
Of the 149 drugs approved in both Canada and the United States between 2005 and 2011/12, approval was granted a median 350 days earlier in the United States. Of the 146 drugs approved in both Canada and Europe, approval was granted a median 263 days earlier in Europe. The more important factor in explaining these delays in access to medicines in Canada is differences in the dates on which manufacturers submitted new drugs to agencies for regulatory approval.

If we constrain our analysis to compare drugs for which submission dates are available, the average 682-day difference in approval dates between Canada and the United States (for 120 drugs) consists of an average 635-day difference between submission dates, and an average 48-day difference in efficiency (figure E1). Similarly, the average 417-day difference in approval dates between Canada and Europe (for 131 drugs) consists of an average 315-day difference between submission dates, and an average 102-day difference in efficiency (figure E1).

Several reasons for this difference in submission may exist, including differences in market-investment attractiveness due to prevalent intellectual property protection regimes, the size 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 market 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 for

Figure E1: Explained average difference in days preceding Canadian approval, by component, 2005-2011/12



Note: Totals may not add up due to rounding

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

One way to reduce the loss of potential benefits from access to newer medicines, at least for Canadians, would be to better recognize that the approach taken by Health Canada is unnecessary and perhaps harmful. Importantly, Health Canada's approval process largely duplicates what is already being done (much earlier and more efficiently) in the US and Europe, which means the benefits of this process for Canadians are limited at best.

Health Canada's approach to scientific review of new drugs is not considerably different from those in the US and Europe (Rawson, 2013; Rawson, 2003; Paul, 2001). Critically, Canadian laws and regulations regarding prescription drugs have generally followed those of the United States (Graham, 2005). Further, there are many similarities between the drug approval processes in Canada, the US, and the EU. 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. Given the low and similar rate of withdrawal of drugs (at least between the US 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 to not be withdrawn from the marketplace. Canadians also, potentially 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 Canadians with fewer therapeutic options and potentially worse health outcomes. Beyond these foregone benefits lie the costs to taxpayers and drug manufacturers of funding this duplicative process.

This provides a strong reason to seriously consider whether or not Health Canada's mandatory approval process is in fact beneficial to Canadians, and to consider replacing Health Canada's mandatory approvals with a mutual recognition process. Under such an approach, FDA or EMA approval decisions could be considered sufficient for market access in Canada. The clear benefits of mutual recognition would be a reduction in costs of entry to the Canadian marketplace and a significant reduction in the delay Canadians endure to access 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, while maintaining Health Canada's approval process on a non-mandatory basis. Specifically, while FDA and EMA approvals could

be accepted as sufficient for market entry, they could also be subject to a labeling requirement stating the approval was through a mutual recognition process with the FDA and EMA and that Health Canada had not approved that particular medicine. This would give Canadians 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 US or Europe. Such reform facilitates earlier access for Canadian patients willing to take on 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 mutual recognition process may provide an opportunity for Health Canada to shift away from performing a largely unnecessary function that may be subject to negative marginal returns, to one whose importance is being increasingly identified. Importantly, the resources saved through the mutual-recognition approach could be in part redirected towards more active post-market surveillance of drug safety and risk. These resources might also be refocused towards 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 tradeoff they are facing when choosing a particular treatment option. With increasingly complex products being approved, such efforts would leave more control of the risk/benefit tradeoff 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 potential benefit to patients.

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, mitigate 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 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 by 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). The efficiency with which these agencies approve drugs and the numbers of drugs ultimately approved varies considerably between these regulatory authorities (see for example, Rawson, 2012; Rawson, 2013; Barua and Esmail, 2013; Downing et al., 2012).

While the potential for harm that accompanies any new medicine on the market may provide some justification for regulatory approval in general, the question of why such approval is duplicated in one jurisdiction (e.g., Canada) while it is being undertaken in another with comparable standards

(e.g. Europe) remains. Indeed, to the extent submissions to these agencies and their efficiency in approving them vary, such duplication of effort reinforces the unfortunate reality that drugs are available to patients in different countries, at different points in time.

This study aims 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 2005-2011/12 (Health Canada moved from calendar-year to fiscal-year reporting in 2011/12), and comparing the corresponding approval dates with those in the United States and the European Union, we seek to 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 in comparison with 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 utilization result in subsequent changes in inpatient care utilization and mortality between 1980 and 1992, Lichtenberg (1996) found that increases in prescription drug use were linked to reductions in the number of hospital bed-days consumed.

The Conference Board of Canada (Hermus et al., 2013) recently 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.

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 of Columbia University, the leading expert in this area, have found that the vintage (or novelty) of drugs consumed is also an important factor in generating health and social benefits.[1]

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.[2]

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 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 US 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.

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 wellbeing 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 larger jurisdictions (in population terms) are already providing reviews of drug safety.

1 As briefly alluded to in the introduction, vintage or novelty refers not only to newer medicines but also to both breakthrough and incremental 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 that 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.

2 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.

Delays in accessing new medicines in Canada

The drug approval process: Differences in efficiency

After passing through the requisite clinical trial process in accordance with basic international scientific standards[3], governments typically subject new drugs 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—which is 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.[4]

In Europe, manufactures have a variety of choices for regulatory approval.[5] Through the Centralized Procedure overseen by the EMA, manufacturers can, by virtue of a single application, receive authorization to market

3 Such as those established by the World Medical Association Declaration of Helsinki (World Medical Association, 1964).

4 See Thaul (2012) for further details.

5 Some drugs are, however, 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).

a medicine to patients and health care professionals throughout the European Economic Area [EEA] (EMA, 2013a). 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,[6] regulatory approval processes are handled with varying approaches and rates of efficiency depending on the government agency involved. Numerous reviews of regulatory agency efficiency have raised important questions about the pace at which Health Canada provides drug approvals.

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 Europe (408 days).

Barua and Esmail (2013) found that Health Canada took a median of 355 days[7] to issue a notice of compliance 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 Europe 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 et al. (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 it 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

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

7 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.

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

Clearly, in simple comparative terms, Health Canada both approves fewer medicines than the FDA or EMA 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 regarding when drugs are eligible for sale in the three regions. Critically, a delay in accessing 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, efficiency comparisons are somewhat hindered when not controlling for the fact that 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. This leads to submission of new drugs by companies to agencies at different times as opposed to concurrent application in all jurisdictions.

Whatever the cause of the total delay, the policy issue is the timeliness of access to medicines for Canadians.

Downing et al (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 US (385 were submitted first in the US), 77% of which (297 drugs) were approved in Canada more than six months after approval in the US. Rawson also notes the proportion of drugs that were approved in Canada more than six months after they were approved in the US 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 6 months for 19 of the 21 drugs, and by more than 18 months for 9.

In order to better capture this important aspect of timely access, the following analysis undertakes 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 publically available information from Health Canada's Annual Drug Submission Performance Reports (2006, 2007, 2008, 2009, 2010, 2011, 2012) and online Summary Basis of Decision (SBD) database (Health Canada, 2013a). US data is from the FDA's online searchable catalogue of approved drug products (FDA, 2013). European data is from the Public Assessment Reports available on the EMA's online searchable catalogue for drugs approved through the centralized procedure (EMA, 2013b) as well as the Mutual Recognition Product Index [MRI] (HMA, 2013).

Method

All drugs (therapeutic and biologic) classified as containing new active substances[8] (NASs) that received approval from Health Canada between 2005 and 2011/12,[9] 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.[10]

Drugs classified as Diagnostic Agents, Diagnostic Radiopharmaceuticals, and Contrast Media were excluded from our analysis, as were Disinfectants, and drugs that appeared to be reformulations or variants of previously approved products (although they may not have been classified as such). An additional 10 pharmaceutical products were excluded from the database due to our inability to clearly identify key regulatory dates, or for which we did not have enough information to perform an exact match (see Appendix B for details).

With regards to the comparison of approval dates, 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 Europe, 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[11] for granting marketing authorization is used. For drugs approved through the mutual recognition procedure in Europe, the "date of outcome" is used.

8 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.

9 Health Canada recently shifted from reporting new drug approvals by calendar year, to reporting by fiscal year.

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

11 Rawson (2012), focusing on delays in patient 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 CHMP opinion date 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 mutual recognition approach rather than delays in access for patients in this study, we follow the approach used by Downing et al.

It should be noted that this 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 Europe, but not Canada. Studies have found that far fewer drugs have been approved in Canada when compared to the United States and Europe in recent years (Downing et al., 2012; Rawson, 2012). Further, we do not include the considerable delays in provincial listing for reimbursement (see for example Rovere and Skinner 2012), which is the point at which access to medicines for Canadians reliant on public programs is possible.

Findings

International differences in patient access to new drugs, 2005-2011/12

There were 154 drugs containing new active substances, and matching our inclusion criteria, granted market authorization by Health Canada between 2005 and 2011/12. Of these, 149 were also granted market authorizing by the FDA for sale in the United States, while 146 were granted market authorization by the EMA for sale in Europe (including 15 drugs that were granted authorization in certain EU countries through the mutual recognition procedure). Two of the 154 drugs (Zeftera and Catena) were approved in Canada but not in the US or Europe.

Drug approval in Canada versus the US:

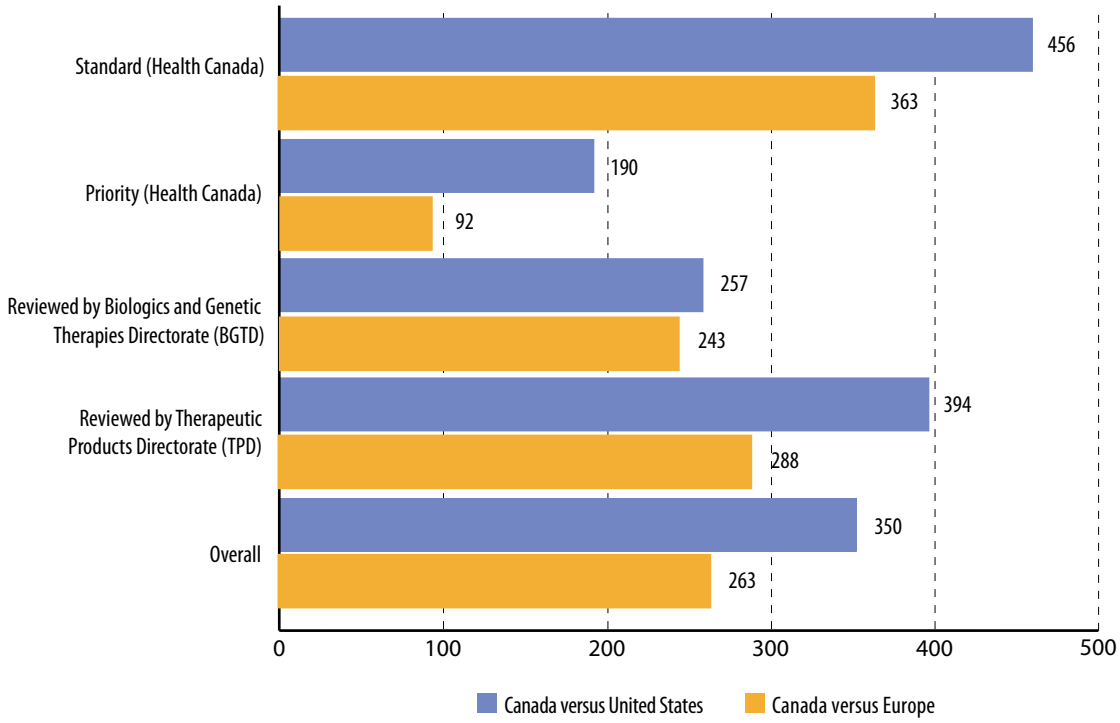
Of the 149 drugs approved in both Canada and the United States, approval was granted a median 350 days earlier in the United States. This difference was larger for the 107 pharmaceuticals reviewed by the TPD (median 394 days) and smaller for the 42 biologic therapies reviewed by the BGTD (median 257 days).

Drugs granted priority status by Health Canada (40 drugs) were approved a median 190 days earlier in the United States, while those subjected to the standard review procedure were approved in Canada a median 456 days after receiving approval in the United States.

Drug approval in Canada versus Europe:

Of the 146 drugs approved in both Canada and Europe, approval was granted a median 263 days earlier in Europe. This difference was larger for 106 pharmaceuticals reviewed by the TPD (median 288 days) and smaller for the 40 biologic therapies reviewed by the BGTD (median 243 days).

Figure 1: Median number of days drugs were approved in the United States and Europe before they were approved in Canada, 2005 to 2011/12



Drugs granted priority status by Health Canada (39 drugs) were approved a median 92 days earlier in Europe, while those subjected to the standard review procedure were approved in Canada a median 363 days after receiving approval in Europe.

Overall, if we consider first approval in either Europe or the United States, patients would receive access to 152 new pharmaceutical therapies (of the 154 in our sample), a median 494 days earlier.[12] 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.

International differences in patient access to new drugs, by therapeutic class, 2005 to 2011/12

Using Anatomical Therapeutic Chemical (ATC) codes, it is possible to categorize drugs in our sample by therapeutic class. Tables 1a and 1b present the differences in patient access to new drugs, by therapeutic class, between Canada and the United States and Europe.

12 As noted above, Rawson (2013) finds the delay in submission in Canada in comparison with the US has been getting longer in recent years.

Table 1a: Median number of days drugs were approved in the United States before they were approved in Canada, by therapeutic class, 2005 to 2011/12

ATC category	Days	Number of drugs
Systemic hormonal preparations, excl. sex hormones and insulins	937	3
Cardiovascular system	892	10
Various	752	6
Nervous system	742	17
Genito urinary system and sex hormones	525	6
Antineoplastic and immunomodulating agents	379	42
Sensory organs	361	5
Dermatologicals	342	1
Musculo-skeletal system	326	2
Alimentary tract and metabolism	324	15
Blood and blood forming organs	181	11
Respiratory system	134	4
Antiinfectives for systemic use	91	27

Table 1b: Median number of days drugs were approved in Europe before they were approved in Canada, by therapeutic class, 2005 to 2011/12

ATC category	Days	Number of drugs
Genito urinary system and sex hormones	1208	6
Systemic hormonal preparations, excl. sex hormones and insulins	735	3
Musculo-skeletal system	543	2
Respiratory system	507	4
Various	475	5
Alimentary tract and metabolism	448	16
Dermatologicals	363	1
Nervous system	351	16
Blood and blood forming organs	293	10
Antineoplastic and immunomodulating agents	253	42
Sensory organs	202	4
Cardiovascular system	168	9
Antiinfectives for systemic use	75	28

As seen in table 1a, the greatest relative lag between Canadian approval and US approval is for medicines related to systemic hormonal preparations (excluding sex hormones and insulins) at 937 days, with the shortest difference in antiinfectives for systemic use (91 days). Table 1b indicates that the greatest relative lag between Canadian approval and European approval is

in medicines related to the genito urinary system and sex hormones (1,208 days); and the shortest lag is again in antiinfectives for systemic use (75 days).

International differences in patient access to new drugs, by year, 2005 to 2011/12

Health Canada approved 31 drugs meeting our inclusion criteria in 2011/12. Thirty of these drugs were also approved in the United States, but were available a median 386 days earlier. All 31 drugs were approved in Europe, and were available a median 267 days earlier (figure 2a). While still considerable, the difference in access is a marked improvement over the 600-day disparity with the United States, and the 488-day disparity in Europe in 2005 (see figures 2b – 2g).

As shown in figures 2a to 2g, in every year between 2005 and 2011/12, nearly every drug examined in this analysis was approved first in the US or Europe. In our sample of 154 drugs, we could identify only three cases (Simponi, Relistor, and Synflorix) over the time period where approval was given by Health Canada before it was approved in either the US by the FDA or in Europe by the EMA (or through the mutual recognition scheme). Further, there were only two drugs (Zeftera and Catena) in our sample that were approved in Canada, but not in either the United States or Europe. Of the 149 drugs approved in both Canada and the United States, only 12 received approval in Canada first. Similarly, of the 146 drugs approved in both Canada and Europe, only 20 received approval in Canada first.

Figure 2a: International differences in regulatory approval for drugs approved in Canada in 2011/12

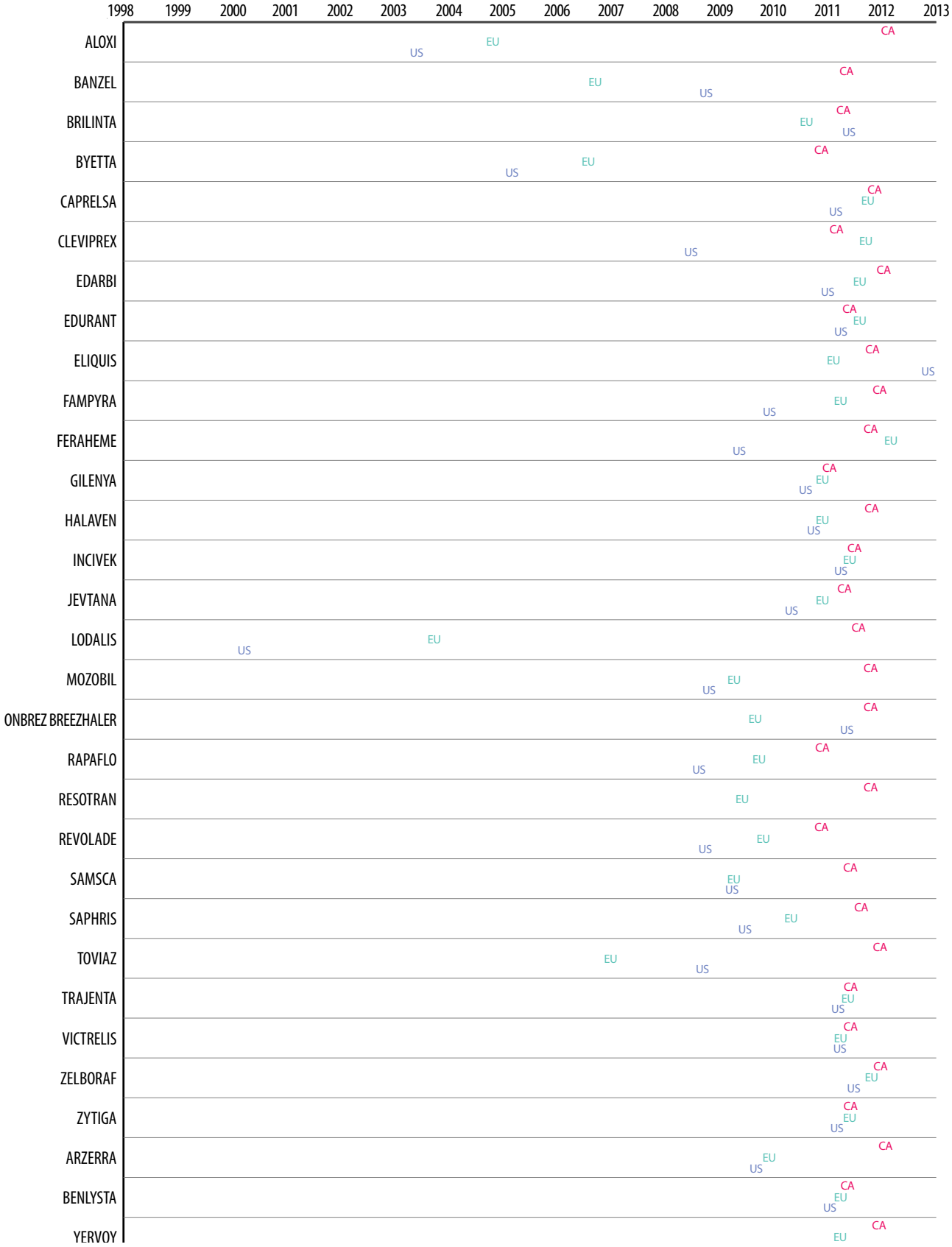


Figure 2b: International differences in regulatory approval for drugs approved in Canada in 2010

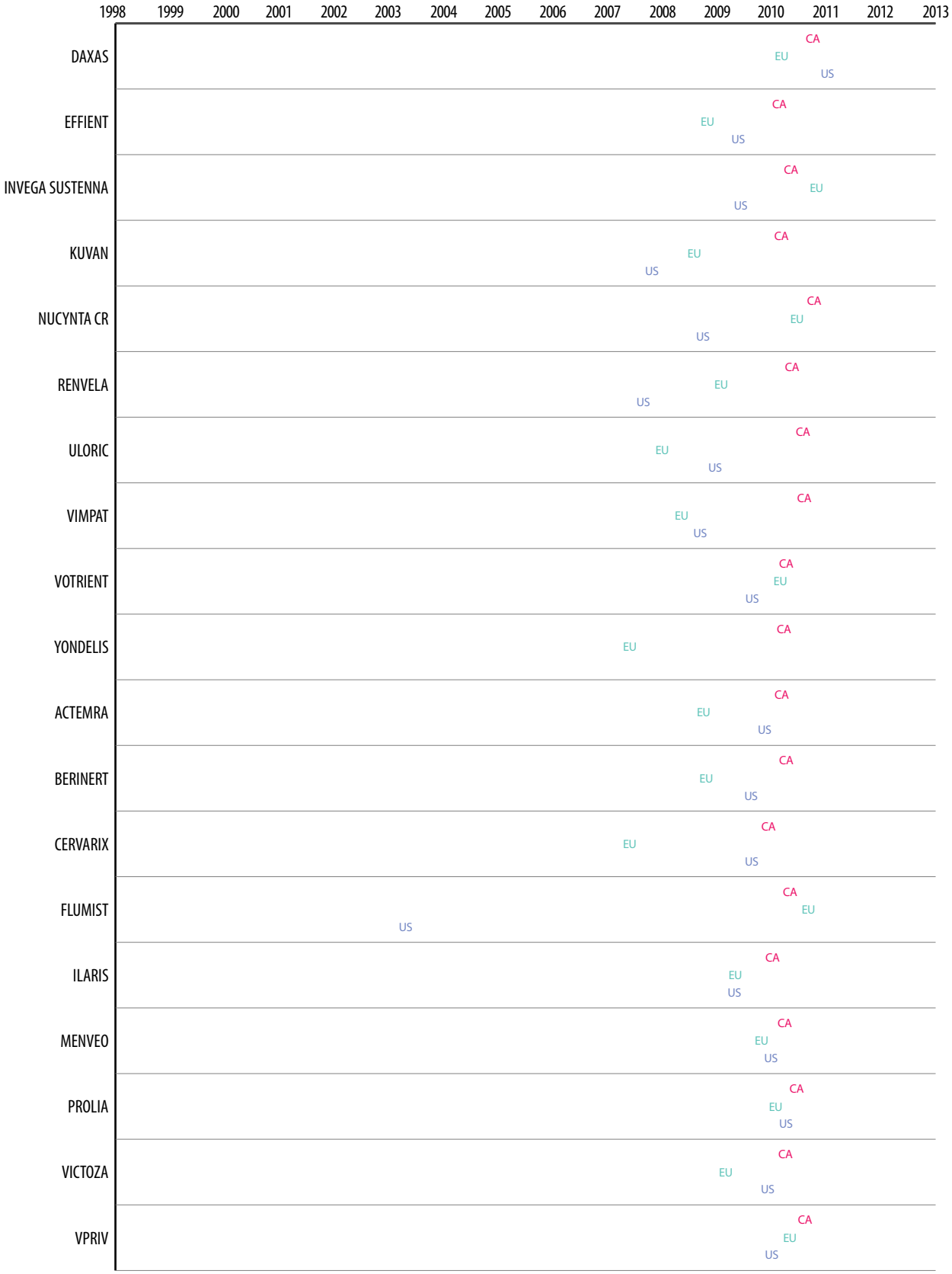


Figure 2c: International differences in regulatory approval for drugs approved in Canada in 2009

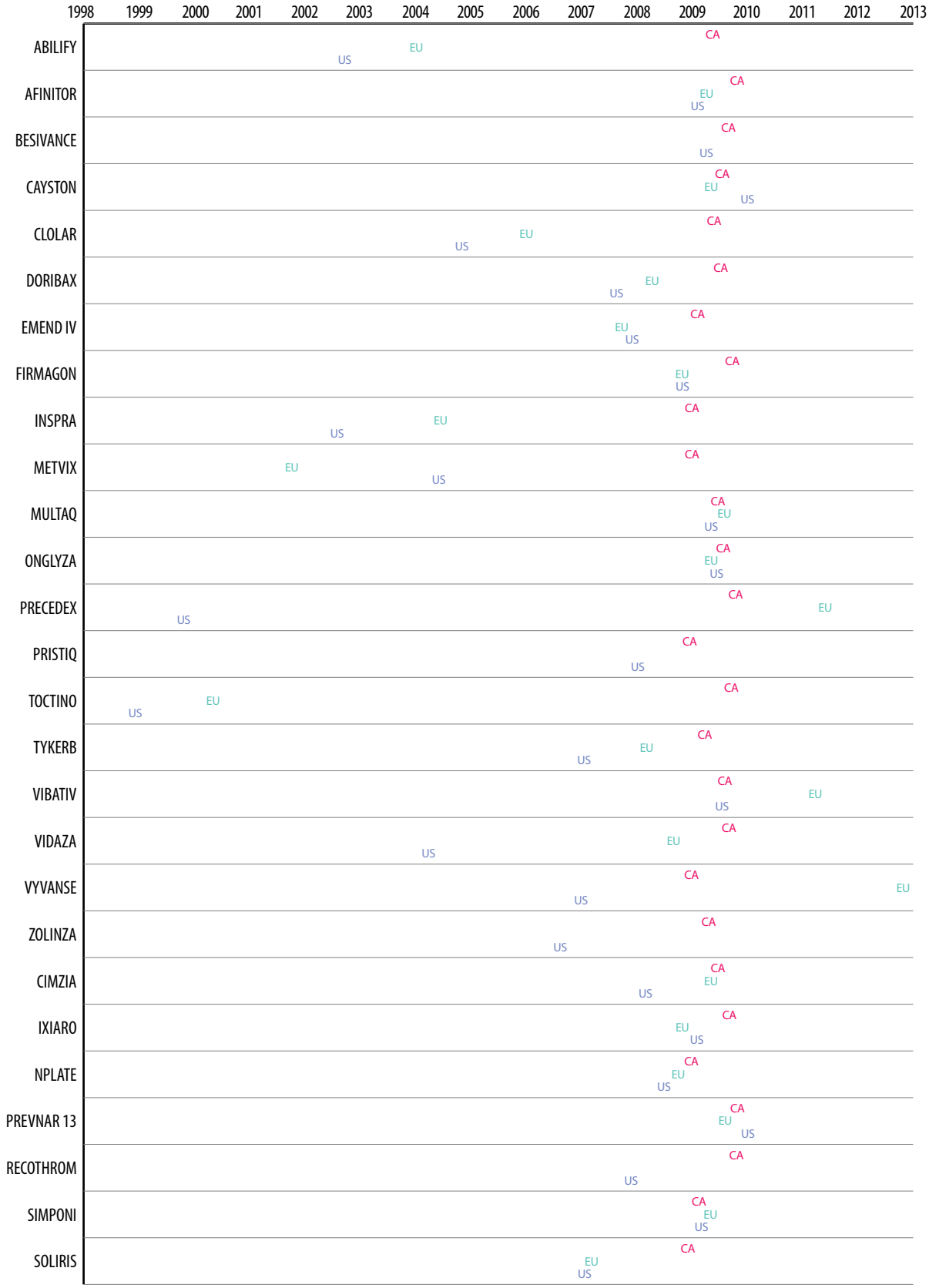


Figure 2d: International differences in regulatory approval for drugs approved in Canada in 2008

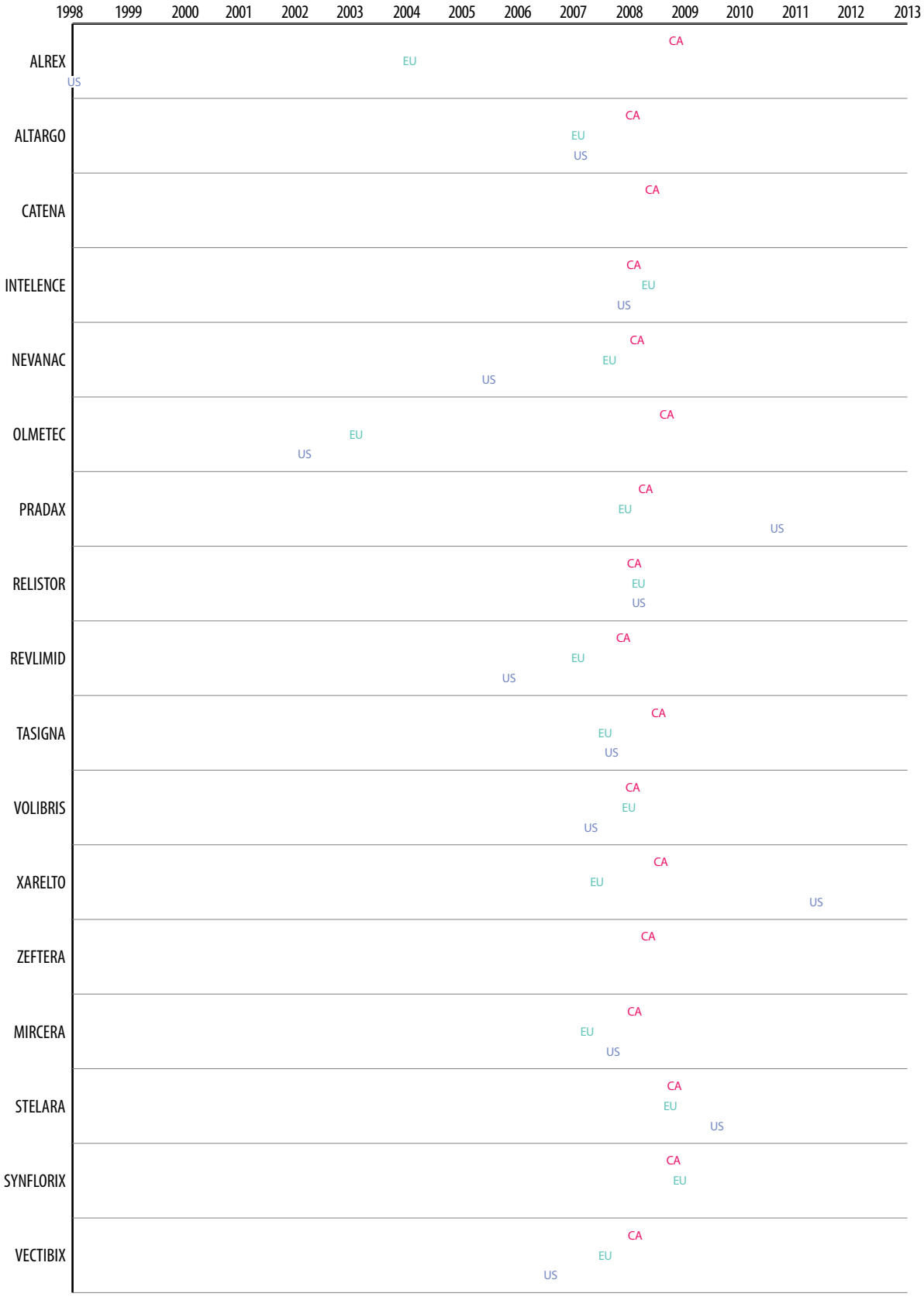


Figure 2e: International differences in regulatory approval for drugs approved in Canada in 2007

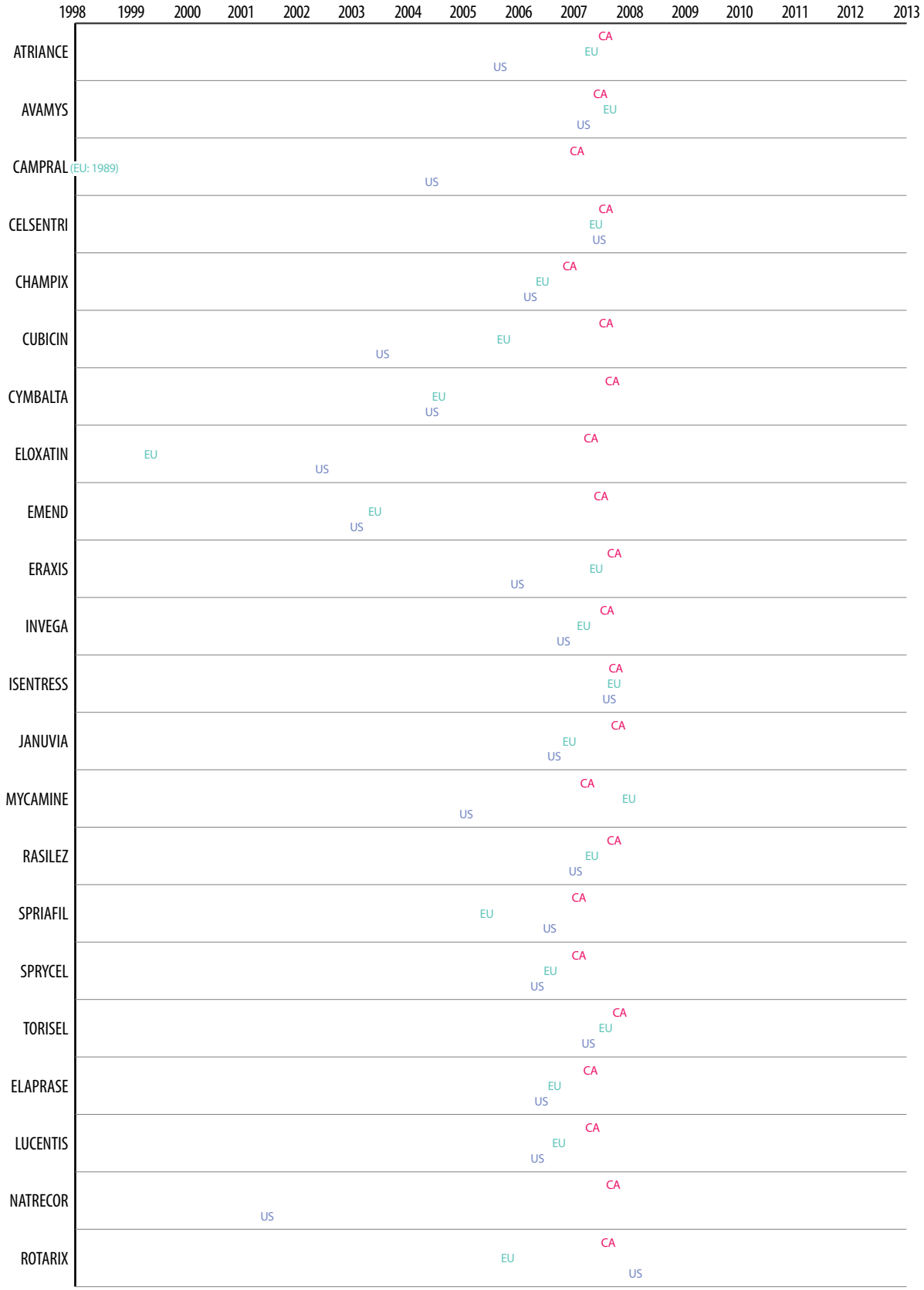


Figure 2f: International Differences in Regulatory Approval for Drugs Approved in Canada in 2006

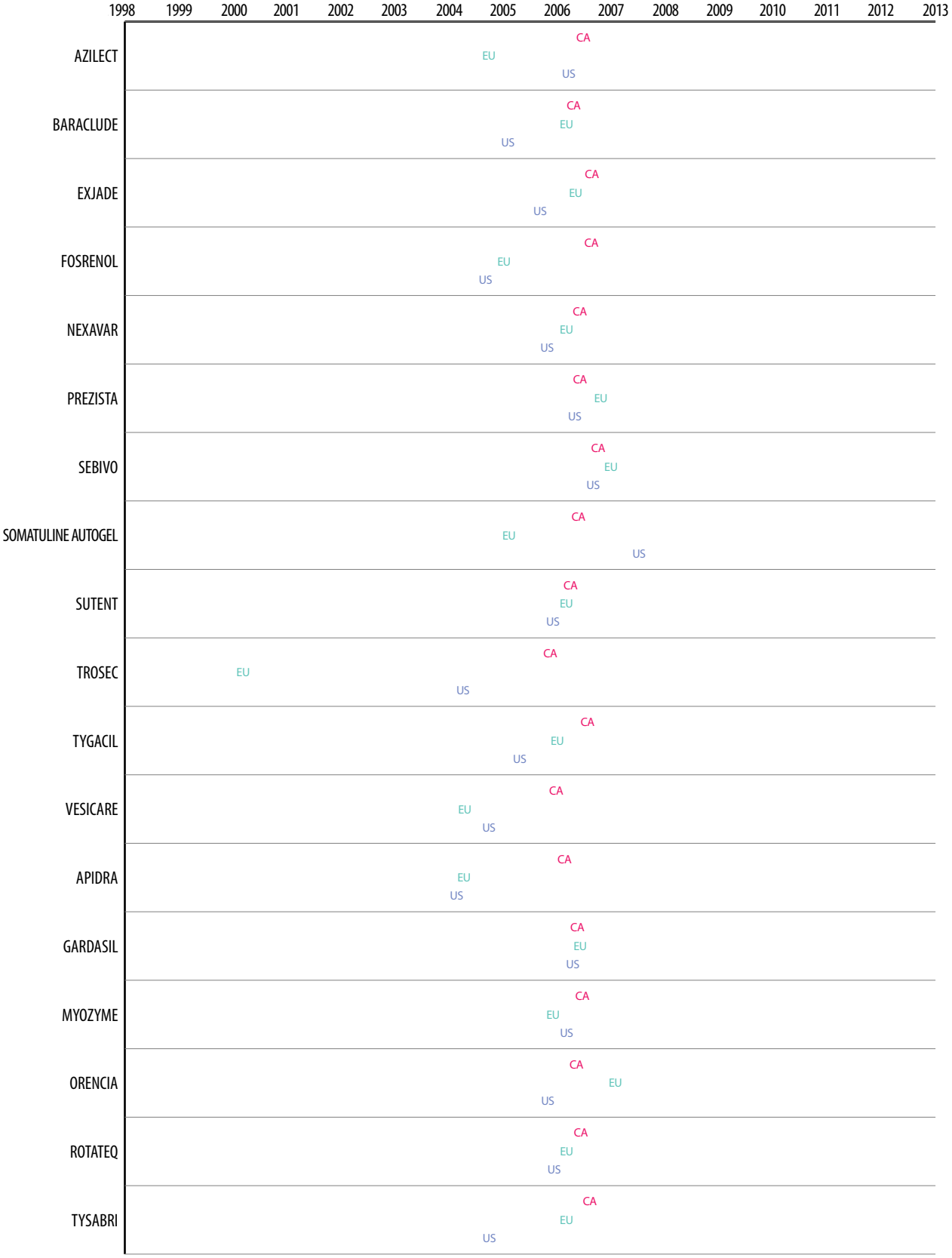
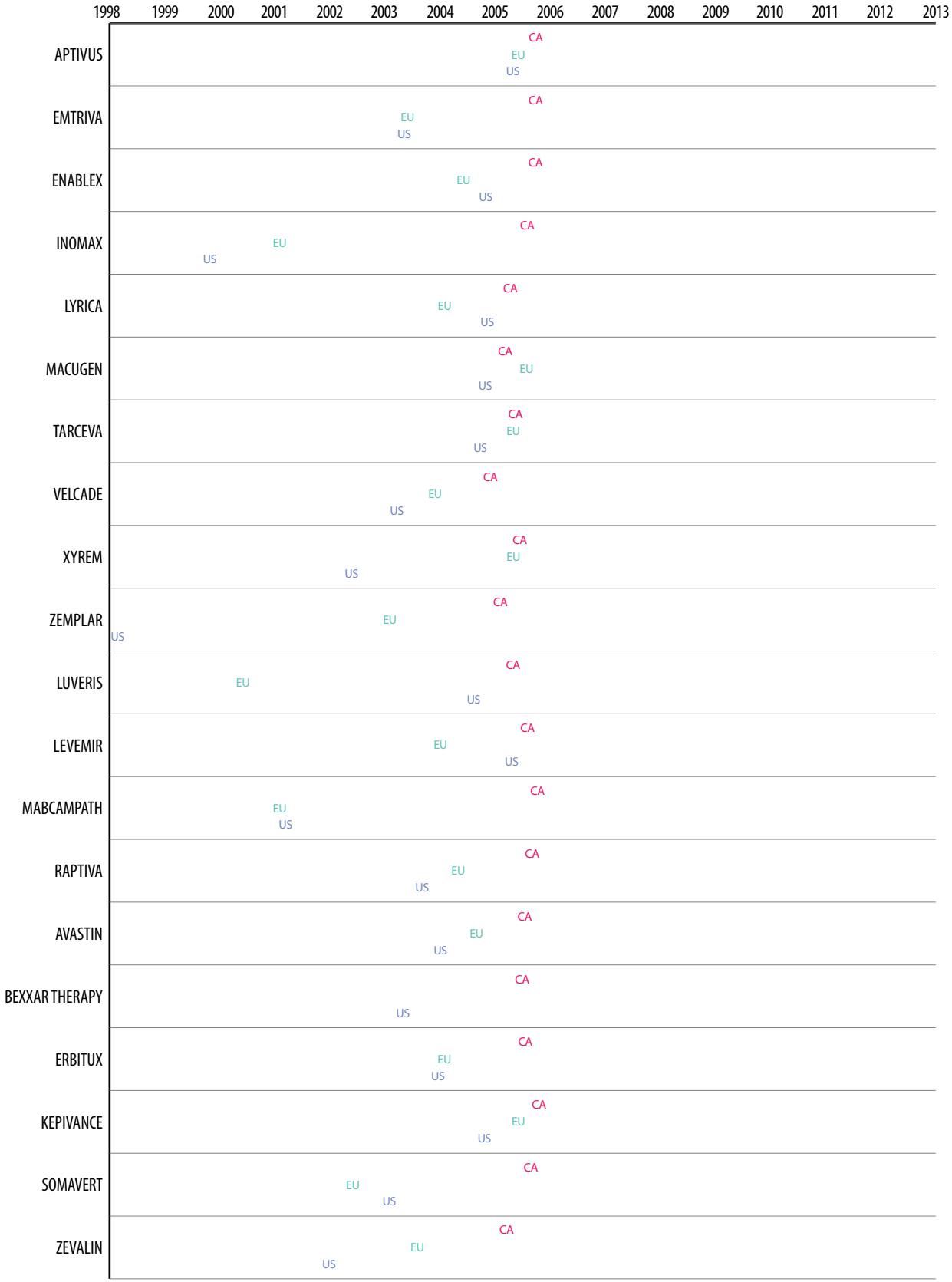


Figure 2g: International differences in regulatory approval for drugs approved in Canada in 2005



Discussion

Submission vs. efficiency

The results above clearly indicate that Canadian patients suffer significantly delayed access to new, innovative medicines relative to their counterparts in the US and Europe.

Some of this delay may be a result of differences in efficiency (Barua and Esmail 2013, Downing et al 2012, Rawson 2012). 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,[13] the average[14] 682-day (342-day median) difference in approval dates between Canada and the United States (for 120 drugs) consists of an average 635-day (237-day median) difference between submission dates, and an average 48-day (71-day median) difference in efficiency.

Similarly, the average 417-day (222-day median) difference in approval dates between Canada and Europe (for 131 drugs) consists of an average

13 In Europe, submission dates are mostly unavailable for drugs approved through the mutual recognition procedure, while in the US they are largely unavailable for biologics. Given that biologics are usually approved quicker than therapeutics, the FDA may appear less efficient than it actually is in the present analysis.

14 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.

315-day (100-day median) difference between submission dates, and an average 102-day (46-day median) difference in efficiency.

Several reasons for this difference in submission may exist, including differences in market-investment attractiveness due to prevalent intellectual property protection regimes, 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 market, in terms of population, 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 for coverage by provincial drug plans and a high rate of refusal to cover, as well as relatively weaker intellectual property protections (Rovere and Skinner, 2012; Esmail, 2013). 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 potentially not submitted for approval in the first place. For example, Downing et al. (2012) analysis 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 of the extent of 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 wellbeing.

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[15] (approved by Health

15 This is also known as sitaxsentan.

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 liver adverse events in some patients (CBC, 2007a, 2007b).[16]

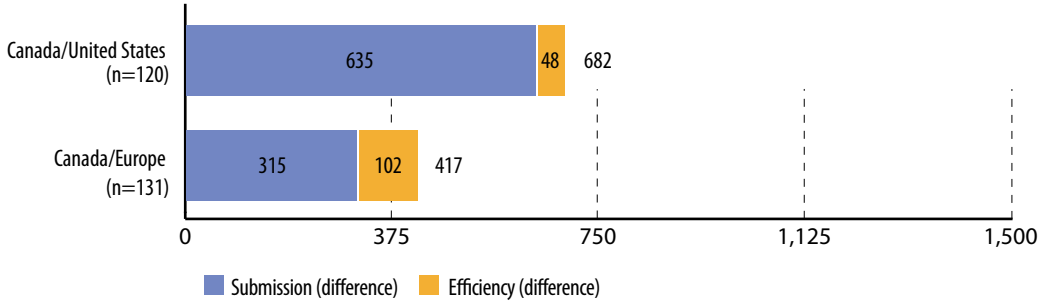
The effects of Type-II errors are much harder to measure. Critically, these drugs do not appear on the market, rendering it impossible to judge the foregone benefits that would have accrued to Canadians. For example, it is not easily possible to quantify the number of Canadian lives lost due to their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

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 former (Type-I) at the expense of the latter (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 due to the problems with measuring such errors noted above.

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 unnecessary and perhaps harmful. The data 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 US or Europe (not counting those medicines never submitted for approval). Yet Health Canada's approval process largely duplicates what is

16 There is also the matter of drugs being pulled from the market due to a perception of unacceptable risk of harm, when some patients would have made different risk/benefit tradeoffs (in a fully informed sense) due to the important positive effects of the medicine. Vioxx and Prepulsid may serve 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 appropriately judge the risk/benefit tradeoff, and whether a centralized judgment by regulators is appropriate for individual patients with varying tolerances of ill-effects and illness, and with varying risk-sensitivities in all cases. The ability of regulators to correctly identify potential risks in the first place is itself also drawn into question when considering the fact that some serious side effects do not become apparent until after a drug has been approved. This is in part because of the limitations of clinical trials in terms of numbers of patients involved and their health and genetic profiles.

Figure 3: Explained average difference in days preceding Canadian approval, by component, 2005-2011/12



Note: Totals may not add up due to rounding

already being done (much earlier and more efficiently) in the US and Europe, which means the benefits of this process for Canadians are limited at best.[17]

It is important to recognize that Health Canada's approach to scientific review of new drugs is not considerably different from those in the US and Europe (Rawson, 2013; Rawson, 2003; Paul, 2001). Critically, Canadian laws and regulations regarding prescription drugs have generally followed those of the United States (Graham, 2005). Further, there are many similarities between the drug approval processes in Canada, the US, and the EU. 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, potentially 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 Canadians with fewer therapeutic options and potentially worse health outcomes. Beyond these foregone benefits lie the costs to taxpayers and drug manufacturers of funding this duplicative process.

The question then must be: why duplicate FDA and EMA processes in Canada? Both the FDA and EMA are well-resourced, highly respected organizations that ostensibly maintain standards of scientific rigor 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 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

17 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).

reviews that are far superior to those provided by the FDA and 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.

Rawson (2013) recently examined safety warnings for 454 medicines approved in Canada and the United States between 1992 and 2011. He found that 2.9% of drugs were discontinued for safety reasons in the US compared to 3.1% in Canada. The 10-year rate of survival without a serious safety warning in the US was 69.3% compared to 58.4% in Canada, though the list of drugs that received warnings did not match in the two countries. While this latter statistic might suggest potential greater rigor at Health Canada, further investigation suggests this may not be the case. As noted above, Health Canada's apparent higher rate of issuing safety warnings may be indicative of a greater aversion to risk/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 US that are yet to be or will ultimately not be approved in Canada and the consequent foregone health benefits (Graham, 2005).[18]

It is this latter point that is most critical in this discussion. As noted above, by far the greatest part of the delay suffered by Canadians in accessing new drugs is the submission delay to Health Canada, which is outside of Health Canada's control. Given the low and similar rate of withdrawal of drugs (at least between the US 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 to not be withdrawn from the marketplace. This provides a strong reason to seriously consider 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 market, there is great value in considering replacing Health Canada's mandatory approvals with a mutual recognition process. Under such an approach, FDA or EMA approval decisions could be considered sufficient for market access

18 An analysis of the appendices in Rawson (2013) shows that 93.8% of drugs approved in Canada were also approved in the US between 1992 and 2011 (not including drugs approved in the US prior to 1992), while 81.9% of drugs approved in the US were also approved in Canada. Importantly, the rate of drugs approved only in the US increased over time, reaching 36.8% in 2007-2011, which may be due to drugs being submitted and approved in the US that are yet to be submitted or are under review in Canada.

in Canada.[19] The clear benefits of such an approach would be a reduction in costs of entry to the Canadian marketplace and a significant reduction in the delay Canadians endure to access new drugs. 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 ability 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 a mutual recognition process with the FDA and EMA and that Health Canada had not approved that particular medicine. This could give Canadians 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 US or Europe. 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.

19 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, which may be the result of differences in risk perception, differences in perceived patient needs, or differences in Type-I and Type-II error making. 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 mutual 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 relative to our simple rule, though it would still (depending on the third agency chosen) likely result in earlier access than under the present duplicative regime.

A new role for Health Canada

A mutual recognition process 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.

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 better track information, and ultimately make recommendations on complex risk/benefit tradeoffs. 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 tradeoff 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 tradeoff 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.

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 (e.g. Canada) after having already been received in another with comparable standards (e.g. Europe) is less justifiable.

Instead of duplicating the activities of other agencies, it makes more sense to simply rely on their expertise by accepting US or European regulatory approvals as sufficient for market access in Canada. This would expedite 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 mutual recognition agreements with Europe and the United States (accepting approval from either body as equivalent), patients could have received access to 152 new pharmaceutical therapies (of the 154 in our sample) a median 494 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 alternatively be put towards activities that are potentially under-supported at present. Importantly, some of the saved resources could be put towards post-market surveillance activities and be used to improve the quality of information about the risk/benefit tradeoff of various medicines for Canadians.

The result of such a mutual recognition approach 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 tradeoffs associated with each for Canadian patients and physicians.

Appendix A: Drugs approved in Canada between 2005-2011/12 included in study, with European and United States equivalents

Medicinal ingredient	Canada	Europe	United States
Abatacept	Orencia	Orencia	Orencia
Abiraterone Acetate	Zytiga	Zytiga	Zytiga
Acamprosate Calcium	Campral	Campral	Campral
Alemtuzumab	MabCampath	MabCampath	MabCampath
Alglucosidase Alfa	Myozyme	Myozyme	Myozyme
Aliskiren Fumarate	Rasilez	Rasilez	Tekturna
Alitretinoin	Toctino	Panretin	Panretin
Ambrisentan	Volibris	Volibris	Letairis
Anidulafungin	Eraxis	Ecalta	Eraxis
Apixaban	Eliquis	Eliquis	Eliquis
Aprepitant	Emend	Emend	Emend
Aripiprazole	Abilify	Abilify	Abilify
Asenapine (As Asenapine Maleate)	Saphris	Sycrest	Saphris
Azacitidine	Vidaza	Vidaza	Vidaza
Azilsartan Medoxomil	Edarbi	Edarbi	Edarbi
Aztreonam	Cayston	Cayston	Cayston
Belimumab	Benlysta	Benlysta	Benlysta
Besifloxacin	Besivance		Besivance
Bevacizumab	Avastin	Avastin	Avastin
Boceprevir	Victrelis	Victrelis	Victrelis
Bortezomib	Velcade	Velcade	Velcade
Cabazitaxel	Jevtana	Jevtana	Jevtana Kit
Canakinumab	Ilaris	Ilaris	Ilaris
Capsular Polysaccharide Of Streptococcus Pneumoniae	Synflorix	Synflorix	
Ceftobiprole Medocaril	Zeftera		
Certolizumab Pegol	Cimzia	Cimzia	Cimzia
Cetuximab	Erbitux	Erbitux	Erbitux
Clevidipine	Cleviprex	Cleviprex	Cleviprex
Clofarabine	Clolar	Evoltra	Clolar
Colesevelam Hydrochloride	Lodalis	Cholestagel	Welchol
Dabigatran Etexilate Mesilate	Pradax	Pradax	Pradax

Medicinal ingredient	Canada	Europe	United States
Daptomycin	Cubicin	Cubicin	Cubicin
Darifenacin Hydrobromide	Enablex	Emselex	Enablex
Darunavir	Prezista	Prezista	Prezista
Dasatinib Monohydrate	Sprycel	Sprycel	Sprycel
Deferasirox	Exjade	Exjade	Exjade
Degarelix Acetate	Firmagon	Firmagon	Firmagon
Denosumab	Prolia	Prolia	Prolia
Desvenlafaxine Succinate	Pristiq	Pristiq	Pristiq
Dexmedetomidine Hydrochloride	Precedex	Dexdor	Precedex
Doripenem Monohydrate	Doribax	Doribax	Doribax
Dronedarone Hydrochloride	Multaq	Multaq	Multaq
Duloxetine Hcl	Cymbalta	Cymbalta	Cymbalta
Eculizumab	Soliris	Soliris	Soliris
Efalizumab	Raptiva	Raptiva	Raptiva
Eltrombopag Olamine	Revolade	Revolade	Revolade
Emtricitabine	Emtriva	Emtriva	Emtriva
Entecavir	Baraclude	Baraclude	Baraclude
Eplerenone	Inspra	Inspra	Inspra
Eribulin Mesylate	Halaven	Halaven	Halaven
Erlotinib	Tarceva	Tarceva	Tarceva
Etravirine	Intelence	Intelence	Intelence
Everolimus	Afinitor	Afinitor	Afinitor
Exenatide	Byetta	Byetta	Byetta
Fampridine	Fampyra	Fampyra	Ampyra
Febuxostat	Uloric	Adenuric	Uloric
Ferumoxytol	Feraheme	Rienso	Feraheme
Fesoterodine Fumarate	Toviaz	Toviaz	Toviaz
Fingolimod Hydrochloride	Gilenya	Gilenya	Gilenya
Five Live Reassortant Rotaviruses	Rotateq	RotaTeq	Rotateq
Fluticasone Furoate	Avamys	Avamys	Veramyst
Fosaprepitant Dimeglumine	Emend Iv	Ivemend	Emend
Golimumab	Simponi	Simponi	Simponi
Human C1 Esterase Inhibitor	Berinert	Berinert	Berinert
Ibritumomab Tiuxetan	Zevalin	Zevalin	Zevalin
Idebenone	Catena		
Idursulfase	Elaprase	Elaprase	Elaprase
Indacaterol (As Indacaterol Maleate)	Onbrez Breezhaler	Onbrez Breezhaler	Arcapta Neohaler
Influenza Virus Type A(H1N1) & Influenza Virus Type A (H3N2) And Influenza Virus Type B	Flumist	Fluenz	Intranasal
Insulin Detemir	Levemir	Levemir	Levemir

Medicinal ingredient	Canada	Europe	United States
Insulin Glulisine (Recombinant Dna Origin)	Apidra	Apidra	Apidra
Ipilimumab	Yervoy	Yervoy	Yervoy
Japanese Encephalitis Vaccine Inactivated Adsorbed	Ixiaro	Ixiaro	Ixiaro
Lacosamide	Vimpat	Vimpat	Vimpat
Lanreotide	Somatuline Autogel	Ipstyl	Somatuline Depot
Lanthanum Carbonate Hydrate	Fosrenol	Fosrenol	Fosrenol
Lapatinib Ditosylate Monohydrate	Tyverb	Tyverb	Tyverb
Lenalidomide	Revlimid	Revlimid	Revlimid
Linagliptin	Trajenta	Trajenta	Trajenta
Liraglutide	Victoza	Victoza	Victoza
Lisdexamfetamine Dimesylate	Vyvanse	Elvanse	Vyvanse
Loteprednol Etabonate	Alrex	Lotemax	Alrex
Lutropin Alfa	Luveris	Luveris	Luveris
Maraviroc	Celsentri	Celsentri	Selzentry
Meningococcal [Group A C W And Y] Oligosaccharides Conjugated To Corynebacterium Diphteriae Crm 197	Menveo	Menveo	Menveo
Methoxy Polyethylene Glycol-Epoetin Beta	Mircera	Mircera	Mircera
Methyl Aminolevulinate Hydrochloride	Metvix	Metvix	Metvixia
Methylnaltrexone Bromide	Relistor	Relistor	Relistor
Micafungin Sodium	Mycamine	Mycamine	Mycamine
Natalizumab	Tysabri	Tysabri	Tysabri
Nelarabine	Atriance	Atriance	Arranon
Nepafenac	Nevanac	Nevanac	Nevanac
Nesiritide	Natrecor		Natrecor
Nilotinib Hydrochloride Monohydrate	Tasigna	Tasigna	Tasigna
Nitric Oxide	Inomax	INOmax	Inomax
Ofatumumab	Arzerra	Arzerra	Arzerra
Olmesartan Medoxomil	Olmetec	Olmetec	Benicar
Oxaliplatin	Eloxatin	Eloxatin	Eloxatin
Palifermin	Kepivance	Kepivance	Kepivance
Paliperidone	Invega	Invega	Invega
Paliperidone Palmitate	Invega Sustenna	Xeplion	Invega Sustenna
Palonosetron Hydrochloride	Aloxi	Aloxi	Aloxi
Panitumumab	Vectibix	Vectibix	Vectibix
Paricalcitol	Zemplar	Zemplar	Zemplar
Pazopanib Hydrochloride	Votrient	Votrient	Votrient
Pegaptanib Sodium	Macugen	Macugen	Macugen

Medicinal ingredient	Canada	Europe	United States
Pegvisomant	Somavert	Somavert	Somavert
Plerixafor	Mozobil	Mozobil	Mozobil
Pneumococcal Conjugate Serotype 1 3 4 5 6A 6B 7F 9V 14 19A 19F 23F 18C And Corynebacterium Diphtheriae Crm-197 Protein	Prevnar 13	Prevnar 13	Prevnar 13
Posaconazole	Spriafil	Noxafil	Noxafil
Prasugrel Hydrochloride	Effient	Efient	Effient
Pregabalin	Lyrica	Lyrica	Lyrica
Prucalopride (As Prucalopride Succinate)	Resotran	Resolor	
Raltegravir Potassium	Isentress	Isentress	Isentress
Ranibizumab	Lucentis	Lucentis	Lucentis
Rasagiline	Azilect	Azilect	Azilect
Recombinant Human Papillomavirus Type 11 L1 Protein Recombinant Human Papillomavirus Type 16 L1 Protein Recombinant Human Papillomavirus Type 18 L1 Protein Recombinant Human Papillomavirus Type 6 L1 Protein	Gardasil	Gardasil	Gardasil
Recombinant Human Papillomavirus Type 16 L1 And 18 L1 Protein	Cervarix	Cervarix	Cervarix
Retapamulin	Altargo	Altargo	Altabax
Rilpivirine Hydrochloride	Edurant	Edurant	Edurant
Rivaroxaban	Xarelto	Xarelto	Xarelto
Roflumilast	Daxas	Daxas	Daliresp
Romiplostim	Nplate	Nplate	Nplate
Rotavirus Vaccine (Rix4414 Strain) Live Oral Attenuated (Human)	Rotarix	Rotarix	Rotarix
Rufinamide	Banzel	Inovelon	Banzel
Sapropterin Dihydrochloride	Kuvan	Kuvan	Kuvan
Saxagliptin Hydrochloride	Onglyza	Onglyza	Onglyza
Sevelamer Carbonate	Renvela	Renvela	Renvela
Silodosin	Rapaflo	Urorec	Rapaflo
Sitagliptin Phosphate Monohydrate	Januvia	Januvia	Januvia
Sodium Oxybate	Xyrem	Xyrem	Xyrem
Solifenacin Succinate	Vesicare	Vesicare	Vesicare
Sorafenib	Nexavar	Nexavar	Nexavar
Sunitinib	Sutent	Sutent	Sutent
Tapentadol Hydrochloride	Nucynta Cr	Plexia	Nucynta
Telaprevir	Incivek	Incivo	Incivek
Telavancin Hydrochloride	Vibativ	Vibativ	Vibativ

Medicinal ingredient	Canada	Europe	United States
Telbivudine	Sebivo	Sebivo	Tyzeka
Temsirolimus	Torisel	Torisel	Torisel
Thrombin Alfa	Recothrom	Recothrom	Recothrom
Ticagrelor	Brilinta	Brilique	Brilinta
Tigecycline	Tygacil	Tygacil	Tygacil
Tipranavir	Aptivus	Aptivus	Aptivus
Tocilizumab	Actemra	RoActemra	Actemra
Tolvaptan	Samsca	Samsca	Samsca
Tositumomab	Bexxar Therapy		
Trabectedin	Yondelis	Yondelis	Yondelis
Trospium Chloride	Trosec	Urivesc	Sanctura
Ustekinumab	Stelara	Stelara	Stelara
Vandetanib	Caprelsa	Caprelsa	Caprelsa
Varenicline Tartrate	Champix	Champix	Chantix
Velaglucerase Alfa	Vpriv	Vpriv	Vpriv
Vemurafenib	Zelboraf	Zelboraf	Zelboraf
Vorinostat	Zolinza	Vorinostat MSD	Zolinza

Appendix B: Drugs approved in Canada between 2005-2011/12, excluded from analysis

Diagnostic agents and contrast media

1 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).

- Leukoscan
- Primovist
- Vasovist
- Ruby-Fill
- Cantrace

2 NASs identified as variants

Excelon Patch: *Though classified as an NAS in Canada, Health Canada's Summary Basis of Decision (SBD) document notes that "Exelon* Patch is a transdermal patch containing the medicinal ingredient rivastigmine, a cholinesterase inhibitor. Rivastigmine is also found in Exelon* capsules and solution, which have been marketed in Canada since 2000 and 2002, respectively" (Health Canada, 2013a). The transdermal patch is also explicitly classified as a "new formulation" by the FDA (FDA, 2013).*

Pantoloc M: *Though classified as an NAS in Canada, Health Canada's Summary Basis of Decision (SBD) document notes that "Pantoloc M™ contains the medicinal ingredient pantoprazole magnesium which is an H+, K+-ATPase inhibitor. The sponsor submitted this application as a newly developed formulation of the currently authorized proton pump inhibitor pantoprazole sodium (Pantoloc)" (Health Canada, 2013a).*

Victrelis Triple: *Though classified as an NAS in Health Canada's Annual Drug Submission Performance Report (Health Canada, 2012), and approved on August 10, 2011, the contained active ingredient (boceprevir) is included*

in the product Victrelis (which, unlike Victrelis Triple, does not include peginterferon alfa-2b ribavirin), approved on July 29, 2011. Victrelis is included in our sample.

3 Drugs withdrawn worldwide by manufacturers

- Thelin
- Prexige

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

- Efracea
- Visanne
- Civanex
- Tramacet
- Coversyl
- Dexilant
- Vantas
- Alvesco

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