# NEW DRUG APPROVAL TIMES AND SAFETY WARNINGS IN THE UNITED STATES AND CANADA, 1992-2011

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## ABSTRACT

### Background
New drug approvals in the US and Canada were reviewed in short-term studies in the 1990s. A database of drugs approved in both countries between 1992 and 2011 exists allowing for a longer time horizon to assess trends.

### Objective
To compare review times of drugs approved in the US and Canada over the 20-year period and their duration on the respective markets until any serious safety risk arose.

### Methods
Data on submission and approval dates and review type were obtained from the regulatory agencies.

### Results
454 drugs were approved in both countries in the 20-year period for which the US median approval time was shorter than the Canadian median by >6 months (382 versus 574 days). Nevertheless, in 2007-11, the median approval times were closer in the two countries (302 and 356 days, respectively). 3% of the drugs were discontinued for safety reasons in both countries. The 10-year survival rate without a serious safety warning was significantly lower in Canada (58.4%) than in the US (69.3%). Being approved in 2002-11 with a shorter review time had the greatest impact on a drug receiving a serious safety warning.

### Conclusions
Overall, new drug approval times in the two countries in the last five years were closer, although some important differences remain so that Canadians still wait longer for some new drugs to be approved. The survival rate of a drug without a serious warning decreased substantially in the last decade in both countries, especially in drugs approved with shorter review times.

**Key Words:** *Drug approval, drug lag, drug safety, black-box warning, Canada, United States*

The process of enacting the fifth version of the Prescription Drug User Fee Act (PDUFA) in 2012 led to renewed attention to new drug approval times in the United States – attention that has been both positive and negative with respect to the impact of user fees on the performance of the Food and Drug Administration (FDA). Some authors have demonstrated that the FDA has continued its international competitive edge in approving new drugs in a timely manner and that the US is commonly the first country in which marketing approval is sought.[1,2] In contrast, others have questioned whether expeditious drug approval times are compromising drug safety.[3]

The extent of the time taken to review new drugs in Canada has been of concern for many

years due not only to drugs being approved later in North America than in Europe in the 1970s and 1980s[4] (resulting in North American therapeutics lagging several years behind Europe[5]) but also to several government reviews of the Canadian drug approval system demonstrating the need for change in order to remove inefficient practices and to provide a more competitive pharmaceutical environment.[6-12] Earlier short-term analyses showed Health Canada had much slower review times than the FDA.[13-17]Although Canada has no act similar to PDUFA, Health Canada introduced a cost-recovery fee structure for the review of new drug applications in the mid-1990s, which included the establishment of service performance standards as part of the process.[18]

A database of new drugs approved in the US and Canada between 1992 and 2011 now exists allowing for a much longer time horizon than the earlier studies to assess trends in the timeliness of the review and approval of drugs in these countries, which have similar scientific approaches to the review of new drugs.[16,19] The objectives of this analysis were to compare the review times of drugs approved in both countries over the 20-year period, to assess the variation in factors such as priority review status and type of drug, and to evaluate the duration of the drugs on the respective markets until any serious safety risk arose and the variables that may impact it. A comparison of the 1992-2001 and 2002-11 periods is of particular interest because several high-profile discontinuations due to safety reasons occurred between 1999 and 2004 (e.g. cerivastatin,[20] cisapride,[21-23] troglitazone[24] and rofecoxib[25]), which may have impacted the timeliness of drug approvals and the propensity for safety warnings.

## METHODS

### Approval Times

The methods used to obtain information on new drugs approved in the two countries between 1992 and 2001 have been described previously.[13-17] Although there were different approaches in each country due to access issues, the data came ultimately from the FDA and Health Canada with the exception of drugs approved in Canada between 1999 and 2001 for which submission dates had to be obtained directly from the relevant companies.

From 2002 onward, data on new drugs approved in the US were extracted from FDA and Pharmaceutical Research and Manufacturers of America (PhRMA) publications which, in more recent years, were available from their respective websites.[26,27] For Canada, information was obtained from Health Canada's annual performance reports. Until recently, these were published on the agency's website but are now only available by direct request.[28] Because submission dates were not included in the reports until 2007, they were obtained directly from Health Canada.

In the earlier studies,[13-17] a "new drug" was defined to be any new therapeutic or prophylactic drug of chemical or biologic origin. This definition excluded new salts, esters, dosage forms and combinations of previously approved drugs as well as diagnostic products. As they were a small proportion of the medications approved during the 20-year period (<4%), vaccines were also excluded in this analysis so that the focus was new therapeutic drugs.

Although the study timeframe was 1992 to 2011, if a drug was approved in one country in this period but before 1992 in the other country, relevant data were included. In addition, in 2011, Health Canada changed from a calendar year reporting basis for its annual performance to a fiscal year. Since information on a small number of new drugs approved in the first quarter of 2012 was available, pertinent data were included.

Each drug's approval time was calculated as the difference between the date on which the relevant regulatory agency accepted the submission and the final approval date. No account was taken of approval cycles or any period in which the regulatory clock was stopped. Median and range of approval times were used as summary statistics due to the non-symmetric nature of the majority of the data. Approval times were compared using the Kruskal-Wallis test with $p<0.01$ as a marker of statistical significance to adjust for multiple comparisons.

### Safety Warnings

Drugs discontinued for safety reasons were identified from the FDA and Health Canada websites[29,30] and publications.[13-17,31,32] A drug was regarded as being discontinued if all forms and

doses were removed from the market. The rates of drugs discontinued for safety reasons in the two countries were compared.

Since discontinued products represent the extreme in drug safety, Begosh et al[33] from the FDA proposed that an analysis of the entry of the first black-box warning (BBW) in the professional Label, which is a "summary of essential scientific information needed for safe and effective use of the drug,"[34] would provide an improved assessment of risk. A BBW is entered in the Label when "special problems, particularly those that may lead to death or serious injury, may be required by the FDA to be placed in a prominently displayed box."[34] BBWs have been used since at least the mid-1970s.[35] The date of the first BBW was obtained from the history of each drug's Label available on the FDA's website.[29] MedWatch (the FDA safety information program)[36] was also used to ensure that the data were as complete as possible.

Canada does not have the same formal BBW system but, when Health Canada considers it necessary, a serious warning is required in the drug's Product Monograph (PM),[37] usually highlighted by a box but also by bold capital letters alone in older PMs. The PM is the Canadian equivalent of the FDA Label. PMs are obtainable from Health Canada's online Drug Product Database,[30] but only the latest version is accessible so that a history of changes is not included. In addition, Health Canada has a webpage of advisories and warnings known as MedEffect Canada,[38] which is similar to MedWatch[36] but is not drug-specific (it includes warnings about drugs, natural health, dental and vision products, medical devices, and hospital and surgical equipment) and has no index to allow searching, making it less user-friendly.

Kaplan-Meier survival analyses were performed using the first serious safety warning or discontinuation for safety reasons as a failure and marketing withdrawal for other reasons or the end of June 2012 as a right-censoring point. The lack of the history of changes in the PMs made an assumption necessary in the Canadian data. If a serious safety warning was in the PM but not in MedEffect and a BBW or a lesser warning for the same problem existed in the US, the date of the earliest relevant American warning was used for the introduction of the Canadian warning, unless the drug was approved in Canada after this date in which case it was assumed that Health Canada would have been aware of the issue during its review and the approval date was used. Although older PMs are not on the Drug Product Database,[30] a special request was sent to Health Canada for all PMs for a 25% sample of the drugs for which the assumption was made in order to assess its validity. Proportional hazards regression analyses were performed for each country to evaluate which variables had the greatest impact on the receipt of a safety warning or discontinuation.

## RESULTS

### Approval Times

Of 584 new therapeutic drugs approved in the 20-year period that satisfied the study definition, 554 (94.7%) were approved in the US and 484 (82.9%) in Canada; 454 (77.7%) were approved in both countries. In each country, the median review time for the country-specific drugs was generally longer than that for the drugs approved in both countries (Appendices A and B), but the only difference that was marginally statistically significant was in priority status drugs in Canada. Nevertheless, the drugs approved in Canada alone constituted just 6.2% of all drugs approved in the country and only varied between 2.1% and 11.0% across the four approval periods, whereas in the US, the corresponding rate was 18.1%, which increased sharply from 8.0% to 36.8% across the four periods.

The median review time in the US was shorter than the Canadian median for the 454 drugs approved in both countries by >6 months (Table 1; $p<0.0001$). The Canadian median approval time was longer in all the sub-categories in Table 1, with particularly large differences in each approval period (except the most recent), standard review drugs, biotechnology products, drugs with US orphan status (Canada does not have an orphan drug program), and drugs in the anti-infective, endocrine/metabolic, musculoskeletal (MSK)/pain, oncology, respiratory/gastrointestinal (GI) and "other" categories. With the exception of the cardiovascular, central nervous system (CNS)/psychiatric, endocrine/metabolic, MSK/pain and respiratory/GI categories, all the differences were statistically significant. Nevertheless, it is

notable that overall median approval times and those for priority review drugs were closer in the two countries in 2007-11, although Canada had 50% less priority status drugs than the US (Table 1).

**TABLE 1** Summary of review times for drugs approved in the United States and Canada

| | | United States | | | Canada | | | p-value |
|---|---|---|---|---|---|---|---|---|
| | | No. | Median | Range | No. | Median | Range | |
| All | | 454 | 382 | 42-3726 | 454 | 574 | 90-5118 | <0.0001 |
| Approval period: | ≤1996 | 162 | 560 | 42-3726 | 130 | 750 | 90-5118 | 0.0011 |
| | 1997-2001 | 135 | 365 | 72-1476 | 134 | 565 | 202-1977 | <0.0001 |
| | 2002-2006 | 90 | 302 | 46-1521 | 94 | 635 | 196-1929 | <0.0001 |
| | ≥2007 | 67 | 302 | 78-1093 | 96 | 356 | 204-1902 | 0.0002 |
| Review type: | Priority | 180 | 232 | 42-2716 | 91 | 277 | 185-1884 | <0.0001 |
| | Standard | 274 | 519 | 87-3726 | 363 | 629 | 90-5118 | 0.0005 |
| Product type: | Biotechnology | 60 | 328 | 111-1476 | 60 | 704 | 208-1977 | <0.0001 |
| | Small molecule | 394 | 388 | 42-3726 | 394 | 562 | 90-5118 | <0.0001 |
| US Orphan drug | Yes | 106 | 347 | 72-3053 | 106 | 448 | 158-1977 | 0.0051 |
| status: | No | 348 | 394 | 42-3726 | 348 | 593 | 90-5118 | <0.0001 |
| Drug type: | Anti-infective | 82 | 330 | 42-1926 | 82 | 498 | 143-2848 | 0.0003 |
| | Cardiovascular | 70 | 530 | 159-3497 | 70 | 618 | 227-4633 | 0.078 |
| | CNS/psychiatric | 67 | 518 | 166-3726 | 67 | 580 | 273-3161 | 0.26 |
| | E/M | 33 | 365 | 167-1053 | 33 | 647 | 211-2045 | 0.010 |
| | MSK/pain | 24 | 304 | 178-2954 | 24 | 561 | 90-5118 | 0.083 |
| | Oncology | 62 | 273 | 46-2716 | 62 | 390 | 158-1490 | 0.0003 |
| | Respiratory/GI | 27 | 545 | 180-1349 | 27 | 708 | 206-1586 | 0.22 |
| | “Other” | 89 | 365 | 87-1476 | 89 | 615 | 208-2958 | <0.0001 |

CNS: Central nervous system; E/M: Endocrine/metabolic; GI: Gastrointestinal; MSK: Musculoskeletal

Between 1992-2001 and 2002-11, changes occurred in new therapeutic drugs approved in both countries (Table 2). The proportions of priority status drugs, biotechnology products and anti-cancer therapies have increased substantially. The rate of drugs with US orphan drug status and drugs in the endocrine/metabolic, MSK/pain and "other" categories also saw an increase. In contrast, the proportions of drugs in the remaining categories declined.

**TABLE 2** Changes in type of drugs between 1992-2001 and 2002-2011

| | | United States | | | | Canada | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 1992-2001 | | 2002-2011 | | 1992-2001 | | 2002-2011 | |
| | | No. | % | No. | % | No. | % | No. | % |
| Review | Priority | 101 | 34.0 | 79 | 50.3 | 39 | 14.8 | 52 | 27.4 |
| type: | Standard | 196 | 66.0 | 78 | 49.7 | 225 | 85.2 | 138 | 72.6 |
| Product | Biotechnology | 21 | 7.1 | 39 | 24.8 | 11 | 4.2 | 49 | 25.8 |
| type: | Small molecule | 276 | 92.9 | 118 | 75.2 | 253 | 95.8 | 141 | 74.2 |
| US Orphan | Yes | 59 | 19.9 | 47 | 29.9 | 55 | 20.8 | 51 | 26.8 |
| drug status: | No | 238 | 80.1 | 110 | 70.1 | 209 | 79.2 | 139 | 73.2 |
| Drug type: | Anti-infective | 57 | 19.2 | 25 | 15.9 | 55 | 20.8 | 27 | 14.2 |
| | Cardiovascular | 55 | 18.5 | 15 | 9.6 | 49 | 18.6 | 21 | 11.1 |
| | CNS/psychiatric | 51 | 17.2 | 16 | 10.2 | 46 | 17.4 | 21 | 11.1 |
| | E/M | 20 | 6.7 | 13 | 8.3 | 17 | 6.4 | 16 | 8.4 |
| | MSK/pain | 14 | 4.7 | 10 | 6.4 | 12 | 4.5 | 12 | 6.3 |
| | Oncology | 30 | 10.1 | 32 | 20.4 | 29 | 11.0 | 33 | 17.4 |
| | Respiratory/GI | 18 | 6.1 | 9 | 5.7 | 18 | 6.8 | 9 | 4.7 |
| | "Other" | 52 | 17.5 | 37 | 23.6 | 38 | 14.4 | 51 | 26.8 |

CNS: Central nervous system; E/M: Endocrine/metabolic; GI: Gastrointestinal; MSK: Musculoskeletal

Of the 454 drugs, 385 (84.8%) were submitted and 386 (85.0%) approved first in the US. Almost half (183; 47.5%) of the 385 drugs submitted first in the US had a submission date that was more than 180 days before the Canadian submission date and a much larger number of drugs (297; 76.9%) were approved in the US more than 180 days before approval in Canada. The proportion of drugs submitted in the US more than 180 days before the Canadian submission increased from 34.5% in the period up to 2000 to 48.4% after 2000, while the proportion approved in the US more than 180 days before Canadian approval increased from 58.7% in the period up to 2001 to 74.7% after 2001.

**Safety Warnings and Discontinuation**

Of the 454 drugs, eleven (cerivastatin, cisapride, efalizumab, grepafloxacin, nefazodone, rofecoxib, sibutramine, tegaserod, troglitazone, trovafloxacin and valdecoxib) were withdrawn for safety reasons in both countries. Tolcapone was discontinued for a safety issue in Canada in 1999 but remains on the market in the US. Aprotinin was suspended for a safety reason in both countries in 2007 and remains off the market in the US but was re-approved in Canada in 2011. Natalizumab was withdrawn in the US in 2005 but was allowed back onto the market the following year and, consequently, was not included (it remained on the Canadian market throughout). Although troglitazone was approved and discontinued in Canada, it was never sold.[32] The rate of discontinuation for safety reasons in drugs approved in both countries over the 20-year period was 2.6% in each country. For all drugs approved in Canada and/or the US, the rates were 3.4% in the US and 3.1% in Canada.

A total of 236 drugs (52.0%) had a serious safety warning or were discontinued for a safety reason in Canada or the US, of which 121 (26.7%) had a serious warning or were withdrawn in both countries. In the US, 158 drugs (34.8%) had at least one BBW or were discontinued (64 (40.5%) had the warning in its FDA Label at the time of approval). For 32 (20.3%) of the 158 drugs, a similar serious warning was not found in the Canadian PM or MedEffect.[38]

In Canada, 199 drugs (43.8%) were either discontinued or had a serious safety warning in the PM or MedEffect, but no corresponding BBW was identified for 78 (39.2%) of them, although a less serious warning was found. For these 78 drugs, the date of the relevant American warning was used for the introduction of the Canadian warning, but for 16 of them, the drug was approved in Canada after the date of the relevant American warning and the approval date was used. The same procedure was used for 32 of the 121 drugs with serious warnings in both countries where the date of the implementation of the serious Canadian warning was unknown. All PMs were obtained from Health Canada for 12 of the 48 drugs for which the assumption was made. Four drugs had a BBW, all of which had a corresponding serious warning in their Canadian PM at the time of approval, and eight had no BBW, seven of which had a serious warning in their original PMs, providing positive support for the assumption.

The rates of survival without a serious safety warning or discontinuation for the two countries are shown in Figure 1. The 10-year survival rate in the US was 69.3%, whereas in Canada it was significantly lower at 58.4% (Table 3). The Canadian survival rate was lower in all the sub-categories in Table 3, except cardiovascular drugs. The difference between the two countries was especially acute in drugs with priority status, shorter review times ($\leq$730 days) and US orphan status, as well as biotechnology and oncology products. Within each country, significantly lower survival rates were found in drugs approved between 2002 and 2011 (log-rank test, $p<0.0001$), priority review drugs ($p<0.01$), biotechnology products ($p<0.0001$), and oncology drugs ($p<0.01$). Significantly lower survival rates were also seen in Canada in drugs with shorter review times ($p=0.0016$) and drugs with US orphan status ($p=0.013$).

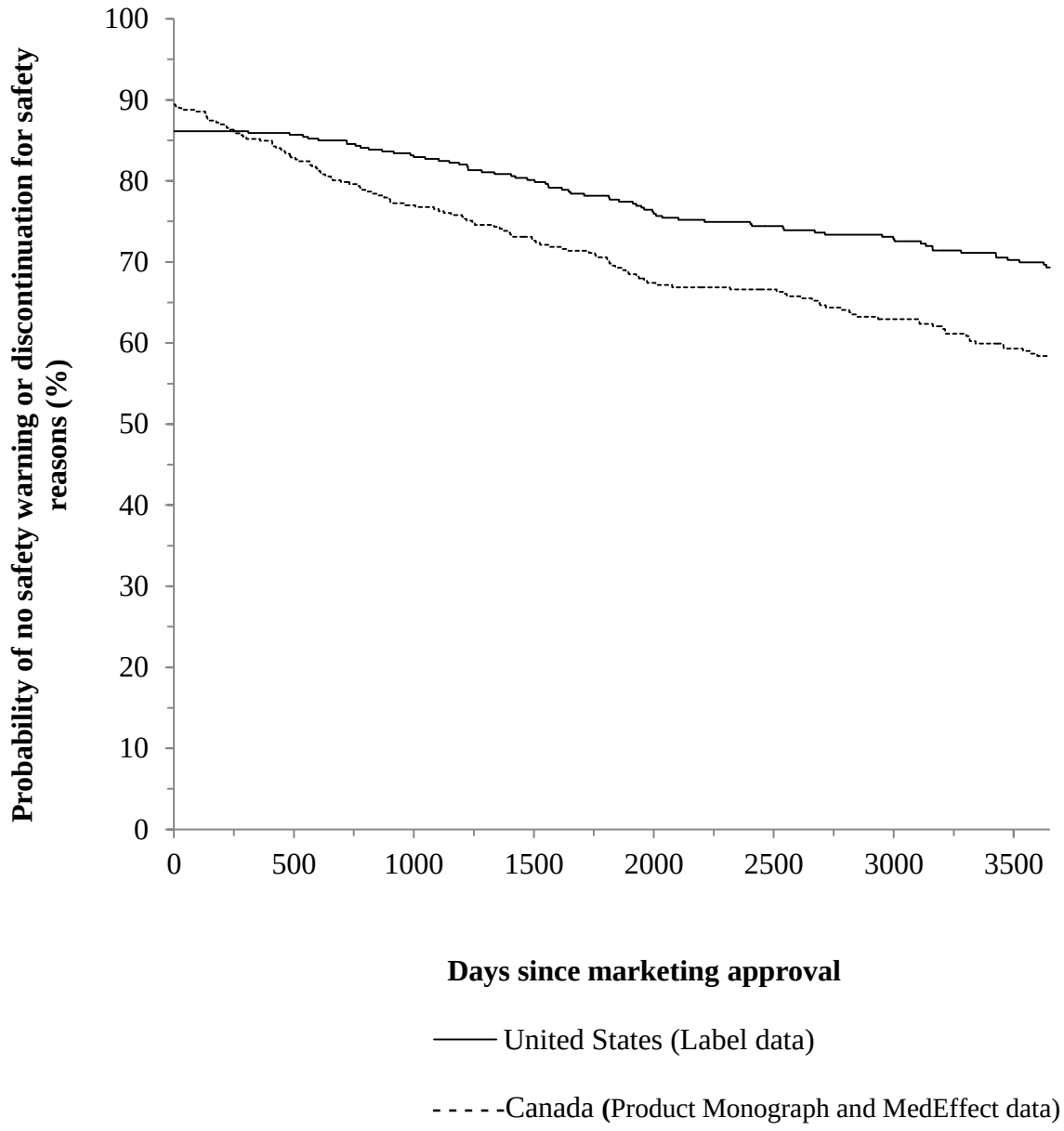
Proportional hazards regression analyses demonstrated that, in both countries, being approved in the last decade had the greatest impact on a drug receiving a serious safety warning (Table 3). In addition, in the US, there was a significantly increased risk of a warning in drugs approved following a short review period, while, in Canada, there was a significantly increased risk in priority status and musculoskeletal drugs.

**TABLE 3** 10-year survival rates without a serious safety warning and results of the proportional hazards regression analyses

| | | United States | | | Canada | | | | United States | | Canada | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No. | Rate (%) | 95% CI | No. | Rate (%) | 95% CI | Log-rank p-value | Hazard ratio | 95% CI | Hazard ratio | 95% CI |
| All | | 454 | 69.3 | 64.6, 73.5 | 454 | 58.4 | 53.3, 63.1 | 0.0007 | | | | |
| Approval | ≤2001 | 297 | 77.3 | 72.0, 81.6 | 264 | 70.2 | 64.2, 75.4 | 0.025 | 1.00 | | 1.00 | |
| period: | ≥2002 | 157 | 56.5 | 47.6, 64.4 | 190 | 41.0 | 32.2, 49.6 | 0.060 | 4.82 | 3.01, 7.72 | 5.98 | 3.95, 9.08 |
| Review | ≤365 days | 215 | 63.8 | 56.4, 70.4 | 121 | 45.4 | 34.6, 55.6 | 0.0022 | 2.65 | 1.53, 4.60 | 1.12 | 0.71, 1.75 |
| time: | 366-730 days | 142 | 71.4 | 63.0, 78.2 | 177 | 55.2 | 47.1, 62.6 | 0.0044 | 1.94 | 1.17, 3.20 | 1.34 | 0.93, 1.93 |
| | >730 days | 97 | 77.5 | 67.5, 84.7 | 165 | 70.1 | 61.9, 76.8 | 0.33 | 1.00 | | 1.00 | |
| Review | Priority | 180 | 60.4 | 52.3, 67.6 | 91 | 33.6 | 23.5, 44.1 | <0.0001 | 1.11 | 0.76, 1.62 | 1.64 | 1.12, 2.41 |
| type: | Standard | 274 | 74.9 | 69.1, 79.7 | 363 | 64.6 | 59.0, 69.6 | 0.0064 | 1.00 | | 1.00 | |
| Product | Biotechnology | 60 | 44.9 | 30.0, 58.7 | 60 | 29.1 | 17.0, 42.2 | 0.12 | 1.11 | 0.69, 1.79 | 0.83 | 0.51, 1.35 |
| type: | Small molecule | 394 | 72.7 | 67.8, 77.0 | 394 | 62.8 | 57.4, 67.7 | 0.0023 | 1.00 | | 1.00 | |
| US Orphan | Yes | 106 | 69.1 | 58.9, 77.3 | 106 | 47.6 | 37.2, 57.3 | 0.017 | 0.64 | 0.41, 0.98 | 0.97 | 0.66, 1.43 |
| drug status: | No | 348 | 69.4 | 64.0, 74.2 | 348 | 61.7 | 55.9, 66.9 | 0.012 | 1.00 | | 1.00 | |
| Drug type: | Anti-infective | 82 | 66.1 | 54.1, 75.6 | 82 | 57.9 | 45.8, 68.2 | 0.32 | 1.13 | 0.55, 2.35 | 1.51 | 0.82, 2.76 |
| | Cardiovascular | 70 | 65.2 | 52.7, 75.2 | 70 | 72.1 | 59.3, 81.4 | 0.56 | 1.20 | 0.58, 2.48 | 1.06 | 0.57, 1.94 |
| | CNS/psychiatric | 67 | 73.1 | 60.3, 82.4 | 67 | 60.1 | 46.0, 71.6 | 0.23 | 0.90 | 0.42, 1.93 | 1.51 | 0.81, 2.84 |
| | E/M | 33 | 76.8 | 57.3, 88.3 | 33 | 54.8 | 34.5, 71.2 | 0.059 | 0.78 | 0.32, 1.93 | 1.16 | 0.56, 2.42 |
| | MSK/pain | 24 | 43.1 | 19.9, 64.4 | 24 | 38.5 | 18.9, 57.8 | 0.67 | 0.88 | 0.38, 2.04 | 2.74 | 1.29, 5.83 |
| | Oncology | 62 | 57.0 | 43.0, 68.8 | 62 | 25.1 | 14.7, 37.0 | 0.0021 | 1.17 | 0.58, 2.36 | 1.36 | 0.76, 2.41 |
| | Respiratory/GI | 27 | 71.2 | 48.5, 85.3 | 27 | 66.4 | 43.6, 81.7 | 0.11 | 1.46 | 0.54, 4.00 | 0.94 | 0.45, 1.99 |
| | "Other" | 89 | 84.7 | 75.1, 90.8 | 89 | 75.7 | 64.3, 84.0 | 0.15 | 1.00 | | 1.00 | |

CI: Confidence interval; CNS: Central nervous system; E/M: Endocrine/metabolic; GI: Gastrointestinal; MSK: Musculoskeletal

**FIG. 1** Kaplan-Meier estimate of a new therapeutic drug surviving without a safety warning or discontinuation



## DISCUSSION

This study of 454 new therapeutic drugs approved in both Canada and the US over a 20-year period provides insight into the similarities and differences between the two countries that earlier short-term annual comparisons do not. When a significant lag occurs, the overlap of drugs between countries in each year is usually small so that the approval times being compared are for different products. In addition, comparing different drugs approved in the two countries (even if significant overlap occurs) can lead to biased conclusions, especially when evaluating safety warnings. The present study is a large inclusive comparison of the review times of the same therapeutic drugs approved in both countries, as well as an analysis of what happens to them in terms of safety discontinuations and warnings over a 10-year period. Nevertheless, it is important to note that differences exist between the two countries in terms of fiscal and human resources[39,40] and the relative importance of their pharmaceutical markets within the global setting (the US constitutes over 30%, whereas Canada represents 1-2%).

Given the difference between the sizes of the two markets, it was predictable that most therapeutic drugs were approved in the US. However, over 87% of the drugs approved in the US also received approval in Canada during the 20-year period. Between 1992 and 2011, the median review time in the US was significantly shorter than the median in Canada, but the Canadian median moved closer to the American figure in the last 5 years. Nevertheless, some important differences remain, especially in oncology drugs which, in 2007-11, had a median approval time in the US of 230 days compared with 362 days in Canada. The difference in oncology drugs has been reported previously,[41] where it was shown that, of 33 new oncology drugs approved between 2003 and 2011, 30 were approved in the US, 26 in the European Community and just 24 in Canada with median review times of 182, 410 and 356 days, respectively; 23 of the 24 approved in Canada had longer review times than in the US and 91% were approved in Canada more than 180 days after US approval. Due to the increasingly later submission of drugs for regulatory review in Canada compared with the US, Canadians are waiting longer for some new drugs, especially drugs in the oncology, endocrine/metabolic and "other" categories (the latter includes several specialty drugs for rare conditions).

A significant change in the last decade has been the substantial increase in the number of novel biotechnology products. Many of these are intended for uncommon cancers or rare disorders for which there is either no therapy or the current treatment has limited effectiveness.[42] Another important change has been the 1.5 to 2-fold increase in the proportion of drugs receiving a priority review. The timely review of drugs aimed at illnesses for which other therapies are not available has been a priority for Health Canada since at least 2002.[39] However, twice as many drugs received priority status in the US as in Canada over the two decades.

Although delaying access to new important drugs can have a major negative impact on patient health,[43] concern has been expressed in both the US and Canada that more rapid drug approvals may lead to an increased risk of safety issues.[3,44] The rate of discontinuation for safety reasons was 3% in both countries, which is consistent with earlier estimates.[17,33] Since the focus of this study was drugs approved in both countries, one would expect the rate of discontinuation to be the same because regulatory agencies are generally consistent in their actions concerning such drugs. The rate of survival without the introduction of a BBW was proposed as a more comprehensive assessment of risk by FDA authors, who found that priority status drugs approved in the US between 1981 and 2005 had a significantly "higher hazard of a safety event" requiring a BBW because "these drugs, with their ability to provide a novel therapeutic benefit, may also involve unusual risk."[33]

Ten years after marketing approval in the US, the 454 drugs in this study had an estimated survival rate without a BBW or discontinuation for safety reasons of 69.3%, which is lower than the 25-year survival rate of 80% reported in an earlier study of the period 1975-99.[35] In Canada for the same drugs, the estimated survival rate was 58.4%. Recently, Lexchin[44] estimated the survival rate without a serious warning in Canada to be

76% for drugs approved between 1995 and 2010 based on safety information from MedEffect.[38] Using MedEffect data only in the present study gave a similar rate of 75%. The Canadian survival rate is significantly overestimated if PM data are omitted.

The survival rate without a serious warning decreased substantially in the last decade to 56.5% in the US and 41.0% in Canada from 77.3% and 70.2%, respectively, in the previous 10 years. In both countries, the survival rate is lower in drugs with shorter review times, priority status drugs, biotechnology products and oncology drugs. It is particularly noteworthy that the proportion of new drugs in the US with a BBW in their Label at approval increased from 5.1% in 1992-2001 to 31.2% in 2002-11, while in Canada, the estimated proportion with a serious warning at approval increased from 2.3% to 22.1%. The change in the 10-year survival rate without a serious warning between the two decades was especially acute in Canada in priority status drugs (50.3% to 22.0%) and drugs with a review times of ≤365 days (61.1% to 34.2%) and 366-730 days (65.0% to 34.1%).

Patients and healthcare providers, as well as pharmaceutical companies, want new drugs for life-threatening or debilitating diseases to be available as soon as is safely possible,[45] especially where no current treatment exists or it has limited effectiveness. Regulatory agencies are cognizant of this need and respond by prioritizing drugs that they assess to be potentially beneficial.[39] This is not an easy task. When five expert clinical pharmacologists from Canada and the US were asked to evaluate the clinical significance (including whether an expedited review was appropriate) of 146 new drugs approved in both countries, the concordance between their assessments was poor and large variation existed in which products were considered to be of sufficient importance for priority status.[46] Post-approval hindsight may suggest that many prioritized drugs do not live up to expectations,[44] but regulatory agencies have to make decisions with imperfect pre-marketing efficacy and safety information.[47]

To enable timely approval of innovative products in this situation, the FDA and Health Canada appear to have increasingly required serious warnings over the last decade, frequently at the time of approval, which may be the outcome of several high-profile withdrawals for safety reasons between 1999 and 2004. Health Canada, in particular, has intensified its use of serious warnings. Almost 40% of the drugs with a serious safety warning in Canada did not have a BBW in the US compared with 23% with a BBW that did not have a serious warning in Canada but did have a less severe warning. Because there has been an increase in the proportion of new priority status drugs that may involve unusual risk,[33] the increased use of serious warnings has been interpreted as implying that unsafe drugs are being approved.[44,48,49] Evidence to support this interpretation in terms of health outcomes studies or drugs withdrawn for safety reasons is not apparent. For example, in the present study, the rate of discontinuation for safety reasons in 2002-11 in drugs approved in the same period was 1.3% in the US and 2.1% in Canada, which was marginally less than the corresponding rates of 1.7% and 2.3%, respectively, in 1992-2001.

Other reasons exist for the increased use of serious warnings. Following several high-profile discontinuations due to safety reasons between 1999 and 2004,[20-25] regulatory agencies may be applying caution when dealing with innovative pharmacologically-complex drugs that have the potential to provide novel benefits but may also have unfamiliar risks, or the agencies may simply be trying to provide more relevant information to allow patients and healthcare providers to make more informed decisions about the use of new drugs. The increase in Canada could also be a response to criticism received by Health Canada regarding the timeliness and adequacy of its communication about drug safety warnings following a well-publicized coroner's inquest into the death of a teenage girl while taking cisapride.[21-23] Whatever the reasons for the increase, serious warnings should be employed wisely to strike an appropriate balance between failing to warn about drug risks and causing warning fatigue.

After many years of slower approval times, overall new drug review times in Canada in the last five years were closer to those in the US. Nevertheless, some important differences remain which, together with generally later new drug

applications, can result in Canadians waiting longer for new drugs. The survival rate of drugs without a serious warning has decreased substantially in recent years in both countries, especially in those with shorter review times. Further research is needed to assess whether the increased use of serious warnings about safety risks leads to more appropriate use of new drugs and to evaluate their actual risk.

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## **APPENDIX A** United States approval times for drugs approved in both countries and those approved in the US only

| | | United States approval times for drugs approved in: | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Both countries | | | United States only | | | |
| | | No. | Median | Range | No. | Median | Range | p-value |
| All | | 454 | 382 | 42-3726 | 100 | 421 | 139-2499 | 0.54 |
| Approval period: | ≤1996 | 162 | 560 | 42-3726 | 14 | 732 | 183-2499 | 0.49 |
| | 1997-2001 | 135 | 365 | 72-1476 | 23 | 483 | 139-1655 | 0.061 |
| | 2002-2006 | 90 | 302 | 46-1521 | 24 | 476 | 177-1827 | 0.049 |
| | ≥2007 | 67 | 302 | 78-1093 | 39 | 302 | 149-2374 | 0.78 |
| Review type: | Priority | 180 | 232 | 42-2716 | 39 | 235 | 139-1827 | 0.25 |
| | Standard | 274 | 519 | 87-3726 | 61 | 530 | 182-2499 | 0.75 |
| Product type: | Biotechnology | 60 | 328 | 111-1476 | 13 | 183 | 166-674 | 0.043 |
| | Small molecule | 394 | 388 | 42-3726 | 87 | 470 | 139-2499 | 0.16 |
| Drug type: | Anti-infective | 82 | 330 | 42-1926 | 13 | 358 | 178-2499 | 0.37 |
| | Cardiovascular | 70 | 530 | 159-3497 | 15 | 672 | 182-2374 | 0.42 |
| | CNS/psychiatric | 67 | 518 | 166-3726 | 12 | 580 | 302-1196 | 0.95 |
| | E/M | 33 | 365 | 167-1053 | 5 | 497 | 273-1559 | 0.33 |
| | MSK/pain | 24 | 304 | 178-2954 | 7 | 512 | 393-1827 | 0.13 |
| | Oncology | 62 | 273 | 46-2716 | 14 | 195 | 149-1078 | 0.94 |
| | Respiratory/GI | 27 | 545 | 180-1349 | 9 | 646 | 177-1425 | 0.78 |
| | “Other” | 89 | 365 | 87-1476 | 25 | 302 | 139-1655 | 0.12 |

CNS: Central nervous system; E/M: Endocrine/metabolic; GI: Gastrointestinal; MSK: Musculoskeletal

## **APPENDIX B** Canadian approval times for drugs approved in both countries and those approved in Canada only

| | | Canadian approval times for drugs approved in: | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Both countries | | | Canada only | | | |
| | | No. | Median | Range | No. | Median | Range | p-value |
| All | | 454 | 574 | 90-5118 | 30 | 731 | 271-2555 | 0.022 |
| Approval period: | ≤1996 | 130 | 750 | 90-5118 | 16 | 888 | 472-2555 | 0.14 |
| | 1997-2001 | 134 | 565 | 202-1977 | 5 | 722 | 478-2454 | 0.12 |
| | 2002-2006 | 94 | 635 | 196-1929 | 2 | 794 | 352-1235 | 0.73 |
| | ≥2007 | 96 | 356 | 204-1902 | 7 | 355 | 271-782 | 0.92 |
| Review type: | Priority | 91 | 277 | 185-1884 | 4 | 1013 | 472-2454 | 0.0090 |
| | Standard | 363 | 629 | 90-5118 | 26 | 719 | 271-2555 | 0.37 |
| Product type: | Biotechnology | 60 | 704 | 208-1977 | 1 | 1235 | - | 0.14 |
| | Small molecule | 394 | 562 | 90-5118 | 29 | 722 | 271-2555 | 0.023 |
| Drug type: | Anti-infective | 82 | 498 | 143-2848 | 3 | 1919 | 346-1937 | 0.12 |
| | Cardiovascular | 70 | 618 | 227-4633 | 6 | 662 | 437-1869 | 0.67 |
| | CNS/psychiatric | 67 | 580 | 273-3161 | 3 | 1262 | 271-1315 | 0.61 |
| | E/M | 33 | 647 | 211-2045 | 3 | 854 | 623-1235 | 0.20 |
| | MSK/pain | 24 | 561 | 90-5118 | 1 | 352 | - | 0.33 |
| | Oncology | 62 | 390 | 158-1490 | 6 | 528 | 346-792 | 0.19 |
| | Respiratory/GI | 27 | 708 | 206-1586 | 5 | 832 | 355-2555 | 0.45 |
| | “Other” | 89 | 615 | 208-2958 | 3 | 782 | 722-2454 | 0.17 |

CNS: Central nervous system; E/M: Endocrine/metabolic; GI: Gastrointestinal; MSK: Musculoskeletal

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