

# The impact of proposed price regulations on new patented medicine launches in Canada: a retrospective cohort study

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## Abstract

**Background:** The Patented Medicine Prices Review Board (PMPRB), the agency that regulates the prices of patented medicines in Canada, published proposed amendments to the regulatory framework in December 2017. Because of a series of changes and delays, the revised policy has not yet been finalized. We sought to evaluate the potential early impact of the uncertainty about the PMPRB policy on patented-medicine launches.

**Methods:** We developed a retrospective cohort of patented medicines (molecules) sold in Canada and the 13 countries that the PMPRB currently uses or has proposed to use as price comparators, from sales data from the IQVIA MIDAS database for 2012–2021. The outcome was whether a molecule was launched (i.e., sold) in a specific country within 2 years of its global

first launch (2-yr launch). We compared the change of 2-year launch before (2012–2017) and after the proposed amendments were published (“uncertain period,” 2018–2021) in Canada with the change in the United States and the other 12 countries as a group (“other-countries group”), using interrupted time series and logistic regressions, respectively. We further conducted analyses for each individual country and subgroups by molecule characteristics, such as therapeutic benefit, separately.

**Results:** We included 242 and 107 new molecules launched before publication of the proposed amendments and during the uncertain period, respectively. The corresponding 2-year launch proportions were 45.0% and 30.8% in Canada, 81.4% and 82.2% in the US, and 83.9% and 70.1% in the other-countries

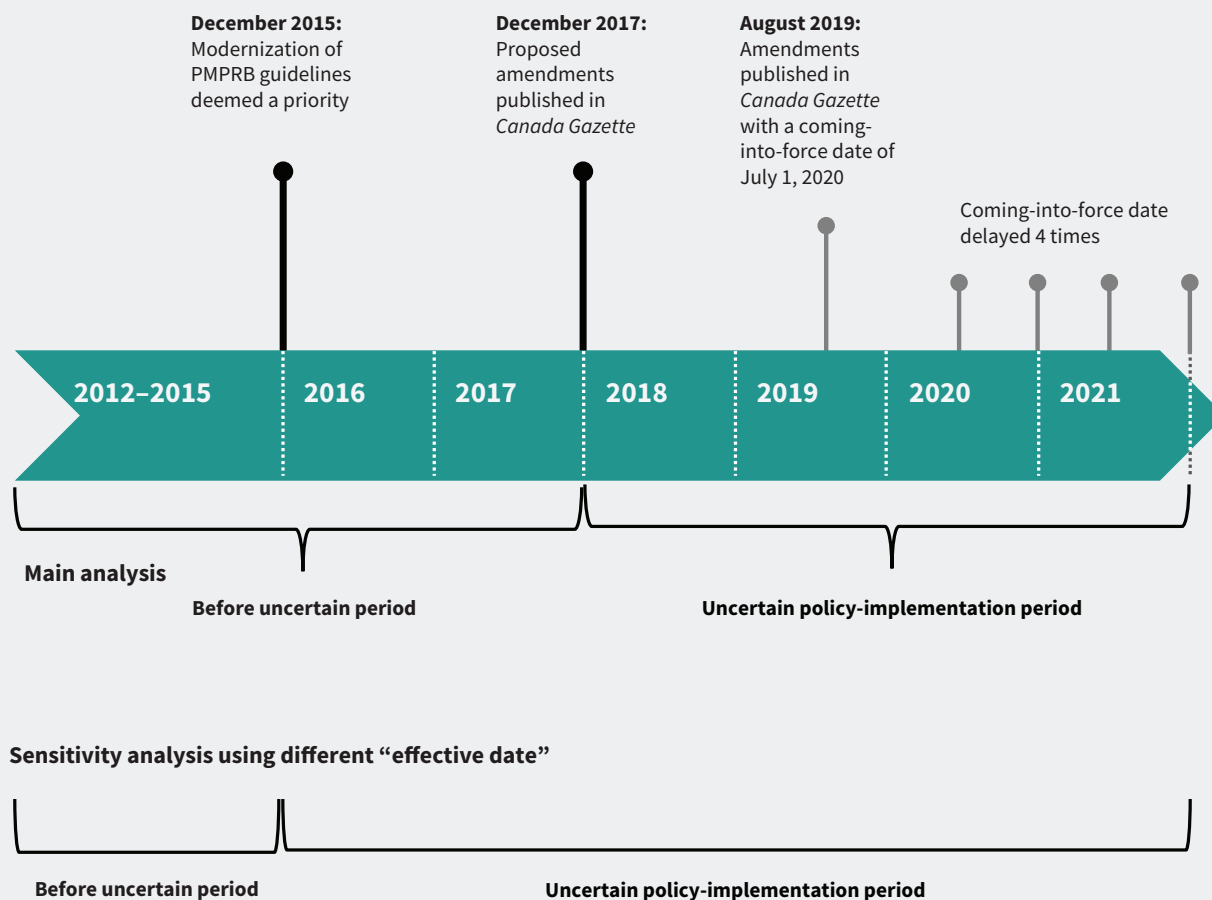
group. All analyses showed changes in 2-year launch during the uncertain period in the US and in the other-countries group that were similar to the changes in Canada. Greater decreases were observed in Norway and Sweden than in Canada. The 2-year launch proportion for molecules with major therapeutic benefit decreased from 45.8% to 31.3% in Canada during the uncertain period and from 87.5% to 62.5% in the other-countries group, but increased from 91.7% to 100% in the US.

**Interpretation:** No negative impact of the PMPRB-policy uncertainty on molecule launches was observed when comparing Canada with price-comparator countries, except for molecules with major therapeutic benefit. The reduction in launches of medicines with major therapeutic benefit in Canada requires continuing investigation.

Since 1987, Canada has regulated the prices of patented medicines to ensure they are not excessive through the Patented Medicine Prices Review Board (PMPRB). Whether the price of a patented medicine sold in Canada is considered excessive depends primarily on the list prices of the same medicine in other comparator countries (external reference pricing) or the list prices of medicines in the same therapeutic class in Canada (internal reference pricing). This regulatory regime has been controversial because of the relatively high costs of patented drugs in Canada.<sup>1,2</sup> Despite the relatively high drug prices, new drug launches in Canada are often delayed, and in many cases, drugs are never

submitted for regulatory authorization in Canada.<sup>3–6</sup> Concerns have been expressed that delayed access to drugs with therapeutic benefit could result in inferior patient outcomes.<sup>7–9</sup> Designing the regulatory system to balance cost and access to new drugs is therefore of great importance.

In December 2015, the PMPRB announced its intention to change Canada’s price regulatory framework (Figure 1 and Appendix 1, available at [www.cmaj.ca/lookup/doi/10.1503/cmaj.231485/tab-related-content](http://www.cmaj.ca/lookup/doi/10.1503/cmaj.231485/tab-related-content)).<sup>10,11</sup> The proposed amendments were published in the *Canada Gazette*, the official newspaper of the Government of Canada, in December 2017.<sup>12</sup> The



**Figure 1:** The timeline of the Patented Medicine Prices Review Board (PMPRB) regulatory amendments. December 2017 is the “effective date” for the period of uncertain policy implementation in the main analyses; December 2015 is the “effective date” in sensitivity analyses.

amendments would, first, change the price comparator countries from the PMPRB7 (France, Germany, Italy, Sweden, Switzerland, the United Kingdom, and the United States) to the PMPRB12 by removing 2 countries with list prices higher than in Canada (the US and Switzerland) and adding 7 countries with prices lower than in Canada (Australia, Belgium, Japan, the Netherlands, Norway, South Korea, and Spain).<sup>2</sup> Second, the amendments would require patentees to report actual transaction prices; these are list prices net of all confidential rebates and discounts that manufacturers pay to drug plans. Finally, the amendments would use new price regulatory factors including pharmaco-economic value, market size, and gross domestic product per capita in Canada.<sup>12</sup>

By Aug. 21, 2019, following some revisions, the regulatory amendments were approved by the federal minister of health and scheduled to come into force July 1, 2020.<sup>13</sup> The key changes were similar to those proposed in December 2017 except that the newer list of reference countries were the “PMPRB11” countries (South Korea was removed).<sup>13,14</sup>

The implementation date of the amendments was postponed 4 times because of the COVID-19 pandemic, feedback from consultations, and a successful court challenge to the requirement that patentees disclose prices net of all adjustments.<sup>10,15–18</sup> In

April 2022, the federal minister of health decided to implement the change in reference countries (PMPRB11) but not the second and third amendments described above.<sup>18,19</sup> The regulatory amendments came into force on July 1, 2022.<sup>18,19</sup> However, the updated guidelines that explain the PMPRB’s approach to the price review process and investigations under the amended regulations have not yet been finalized.<sup>19,20</sup>

Tighter price regulations and lower expected drug prices have been shown to hinder access to new medicines through non-availability and delayed time to launch.<sup>21–27</sup> However, few studies have investigated the impact of price changes or expected price changes within a single country.<sup>28–31</sup> The PMPRB’s own assessment in 2020 found “no early signs that patented medicine price reforms are resulting in fewer new medicines being launched in Canada.”<sup>32</sup> In contrast, assessments conducted or commissioned by industry groups found or projected reductions in the number of drug launches and delays in drug launches in Canada as a result of the proposed amendments.<sup>33–35</sup> However, these assessments were not peer reviewed and did not evaluate the therapeutic importance of the drugs that were not launched.

Gaudette and colleagues found only 1 medicine with added therapeutic benefit among new patented medicines approved in

the US and Europe in 2016–2020 but not submitted for Health Canada review by February 2023.<sup>5</sup> In a cross-sectional study, Lexchin concluded that the “number of therapeutically important medicines not being introduced into Canada is increasing but that is not related to the proposed price reforms.”<sup>36</sup> These analyses were descriptive only, lacked comparisons of the change of launch proportion in Canada with other countries, or did not test the sensitivity of their results by using differing effective dates for the period of policy uncertainty. To address these limitations and provide additional evidence on the issue, we sought to examine empirically whether there was an early impact of the uncertainty around the implementation of drug price regulations or the expected price reduction on new medicine launches in Canada.

## Methods

We conducted a retrospective cohort study of new patented medicines launched (i.e., sold) in 2012–2021 in 14 countries, that is, the combination of PMPRB7 and PMPRB11 (Australia, Belgium, France, Germany, Italy, Japan, the Netherlands, Norway, Spain, Sweden, Switzerland, the UK, and the US) and Canada. We reported the study according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.<sup>37</sup>

Although the PMPRB announced its intention of changing the regulatory framework in December 2015,<sup>11</sup> it is unclear when pharmaceutical companies decided to act or whether they did at all. With the detailed changes published in December 2017,<sup>12</sup> pharmaceutical companies could better estimate the expected price changes for new medicines and take corresponding actions (Figure 1). We therefore selected December 2017 as the “effective” date that pharmaceutical companies were initially exposed to the policy implementation uncertainty (“uncertain period,” 2018–2021). We considered December 2015 as an alternative effective date in sensitivity analyses.

## Data source

Sales data from the IQVIA MIDAS database (formerly IMS) provide sales values and volumes of pharmaceutical products based on detailed audits of the pharmaceutical market through retail and nonretail channels in a corresponding country.<sup>38–40</sup> The core data elements include product name, manufacturer, pack form, strength, and size. MIDAS sales data have been widely used to investigate sales, prices, and launches across countries<sup>5,22–26,28,41,42</sup> and by PMPRB in their annual reports,<sup>2</sup> Meds Entry Watch reports,<sup>43,44</sup> existing guidelines,<sup>45</sup> and research webinars related to their proposed guidelines.<sup>32,46,47</sup> Appendix 2 (available at [www.cmaj.ca/lookup/doi/10.1503/cmaj.231485/tab-related-content](http://www.cmaj.ca/lookup/doi/10.1503/cmaj.231485/tab-related-content)) provides more description on IQVIA MIDAS sales data.

## Study sample

Our study sample comprised all molecules that were “new active substances” and “innovative branded products” categorized in IQVIA MIDAS sales data in the 14 countries in 2012–2021. Innovative branded products included original branded products (manufactured or marketed by the originator), licensed branded prod-

ucts (manufactured or marketed by an official licensee), or other branded products with a known patent protection expiry date.

## Outcomes

The launch date for each molecule in a specific country was determined by its first sale date, as recorded in the IQVIA MIDAS quarterly sales data. The global first launch date was the first sale date in the 14 countries. The main outcome was whether a new molecule was launched in a specific country within 2 years of its global first launch (2-yr launch). We chose a 2-year period because previous studies and our own data have suggested a median time to launch longer than 1 year and a low proportion of domestic launches within 1 year after global launch, in most of our study countries including Canada.<sup>24,43,44,48</sup> Our rationale is outlined in Appendix 3, available at [www.cmaj.ca/lookup/doi/10.1503/cmaj.231485/tab-related-content](http://www.cmaj.ca/lookup/doi/10.1503/cmaj.231485/tab-related-content).

## Variables

We considered variables found to be associated with drug launches in the literature<sup>22–26</sup> as covariates and effect modifiers. Variables comprised the following:

- the first level of the World Health Organization Anatomical Therapeutic Chemical (ATC) classification system, which has 14 main anatomical or pharmacologic groups<sup>49</sup> (each group was considered as a separate category; any groups including  $\leq 5$  molecules in any policy period were combined into the “other ATC” category);
- the number of comparators in Canada (the number of molecules within the same ATC fourth-level chemical, pharmacologic, or therapeutic subgroup that were sold in Canada in the quarter of the global first launch) to indicate the availability of drugs for therapeutic class comparison test conducted by PMPRB and the potential therapeutic advance in Canada (0, 1–4, and  $> 4$ );<sup>45,50</sup>
- high price defined as whether the average price per standard unit of the first globally launched molecule within the first year was in the top 10% among all existing innovative branded molecules in the corresponding launching country and time; and
- the first-year sales in the US (defined as 0 if the molecule was not launched in the US) inflated to 2021 US dollars using the Consumer Price Index ( $> \$20$  million v.  $\leq \$20$  million, a cutoff value close to the overall median).<sup>51</sup>

Detailed definitions and rationales for these variables are presented in Appendix 4, available at [www.cmaj.ca/lookup/doi/10.1503/cmaj.231485/tab-related-content](http://www.cmaj.ca/lookup/doi/10.1503/cmaj.231485/tab-related-content).

We rated each molecule’s therapeutic benefit, using the evaluations, if available, by the PMPRB,<sup>2,45</sup> the Institute for Quality and Efficiency in Health Care (IQWiG),<sup>52</sup> and the independent French medicine bulletin *Prescrire International*.<sup>53,54</sup> As Lexchin did in previous assessments,<sup>36,55</sup> we grouped the ratings of therapeutic benefit into 3 categories: major, moderate, and little to no benefit. If more than 1 of these organizations rated a molecule, we used the highest rating.<sup>36,55</sup> The molecules without ratings from the 3 organizations were rated as major if they were designated as breakthrough therapies by the US Food and Drug

Administration (FDA).<sup>56</sup> More details are presented in Appendix 5, available at [www.cmaj.ca/lookup/doi/10.1503/cmaj.231485/tab-related-content](http://www.cmaj.ca/lookup/doi/10.1503/cmaj.231485/tab-related-content).

### Statistical analysis

Our main analyses focused on the comparisons of Canada versus the US, and Canada versus the “other-countries” group that excluded the US.

We conducted interrupted time series analyses with a control (US or other countries) to compare the outcome in the 2 periods: uncertain period after publication of the proposed amendments (2018–2021) versus before the uncertain period (2012–2017). We used an autoregressive model with maximum likelihood estimation method for the analyses. We then used a bootstrapping approach with 5000 iterations to estimate the confidence interval (CI) of the expected absolute change (predicted – counterfactual) in 2-year launch proportion in Canada and the control, and the difference between the expected absolute changes in Canada and the control.<sup>57</sup> Appendix 6 (available at [www.cmaj.ca/lookup/doi/10.1503/cmaj.231485/tab-related-content](http://www.cmaj.ca/lookup/doi/10.1503/cmaj.231485/tab-related-content)) includes model specification and more details on the analyses.

We further applied a logistic regression by including periods, countries (v. Canada), interaction between countries and periods, and the covariates listed above except for the therapeutic benefit rating because of missing data. We used generalized estimating equation logistic regressions to account for the possible correlation between outcomes from the same molecule. Subgroup analyses were conducted to examine the modifying impact of those covariates.

### Sensitivity analyses

As a sensitivity analysis, we used the proxy measures of first-in-class status and priority review status of FDA approvals<sup>58</sup> to impute the molecules with missing therapeutic benefit ratings. We also reanalyzed our data using December 2015 as the effective date (uncertain period 2016–2021). Additionally, we conducted the comparisons of Canada versus each country and examined the impact on 1-year launch among all study samples.

All of our analyses were performed using SAS version 9.4 (TS1M6) (SAS Institute). We interpreted our results at a *p* value of less than 0.05 and emphasized practical importance for molecules with major benefit.

### Ethics approval

Ethics approval was not required for this study.

## Results

Our cohort included 349 new molecules launched in the 14 countries (242 first launched globally before the uncertain period and 107 during the uncertain period). Correspondingly, 45.0% and 30.8% of these molecules were launched in Canada, 81.4% and 82.2% in the US, and 83.9% and 70.1% in the other-countries group. The characteristics of these molecules are presented in Table 1. The number of launches by country, launch window (1 yr v. 2 yr), and policy period are presented in Appendix 3, Table S1.

Figure 2 presents the observed quarterly 2-year launch proportion and the predicted proportion from the interrupted time series analysis models (Appendix 6, Table S2). The difference between the expected absolute changes in Canada and the US was estimated to be  $-0.066$  (95% CI  $-0.30$  to  $0.15$ ) and the difference between Canada and the other-countries group was  $-0.028$  (95% CI  $-0.25$  to  $0.21$ ) (Appendix Table S3).

The coefficient of the interaction term of comparison country and the uncertain period variables in the logistic regressions indicates the difference between the changes of log odds of launching during the uncertain period (v. before) in the comparison country and in Canada (Table 2 and Appendix 6, Table S4). The interaction term when comparing the US to Canada (coefficient  $0.75$ , standard error [SE]  $0.42$ ;  $p = 0.08$ ) and when comparing the other-countries group to Canada (coefficient  $-0.28$ , SE  $0.36$ ;  $p = 0.4$ ) suggested no difference in the change of log odds of launching in the 2 periods in Canada compared with the US or other-countries group. Similar findings were observed among all the subgroups (Appendix 6, Tables S5–S7).

A total of 244 molecules were rated for their therapeutic value. The 2-year launch proportion for molecules with major benefit decreased from 45.8% to 31.3% in Canada during the uncertain period compared with before the uncertain period, and from 87.5% to 62.5% in the other-countries group but increased from 91.7% to 100% in the US (Table 3). Among molecules with moderate benefit, the launch proportion decreased in all countries: before and during the uncertain period, 93.3% and 83.3% were launched in the US, 97.8% and 91.7% in the other-countries group, and 75.6% and 66.7% in Canada, respectively. The proportion for molecules with little to no benefit decreased in Canada and other countries but increased in the US. The logistic regressions could not be estimated because of the small samples in most of the subgroups (e.g., no nonlaunches in the US after 2017 for molecules with major benefit [Table 3 and Appendix 6, Table S8]).

### Sensitivity analyses

When using December 2015 as the effective date (i.e., the uncertain period was defined as 2016–2021), the 2-year launch proportion by therapeutic value showed a similar trend except that the proportion for molecules with moderate benefit increased in Canada but decreased in the US and the other-countries group (Table 3). The coefficient of the interaction term of the country and period variables ( $3.79$  [SE  $1.66$ ];  $p = 0.02$ ) when comparing the US with Canada suggested that changes in log odds of launching molecules with major benefit after 2015 were different between the 2 countries (Appendix 6, Table S8). However, after further imputing missing ratings using proxy measures, no detectable difference was observed between the change in Canada and the change in the US or the other-countries group for each therapeutic benefit subgroup (Appendix 6, Tables S8 and S9).

We observed some differences in the logistic regression results among subgroups when using December 2015 as the effective date, compared with our results using December 2017. The coefficient of the interaction term between country and

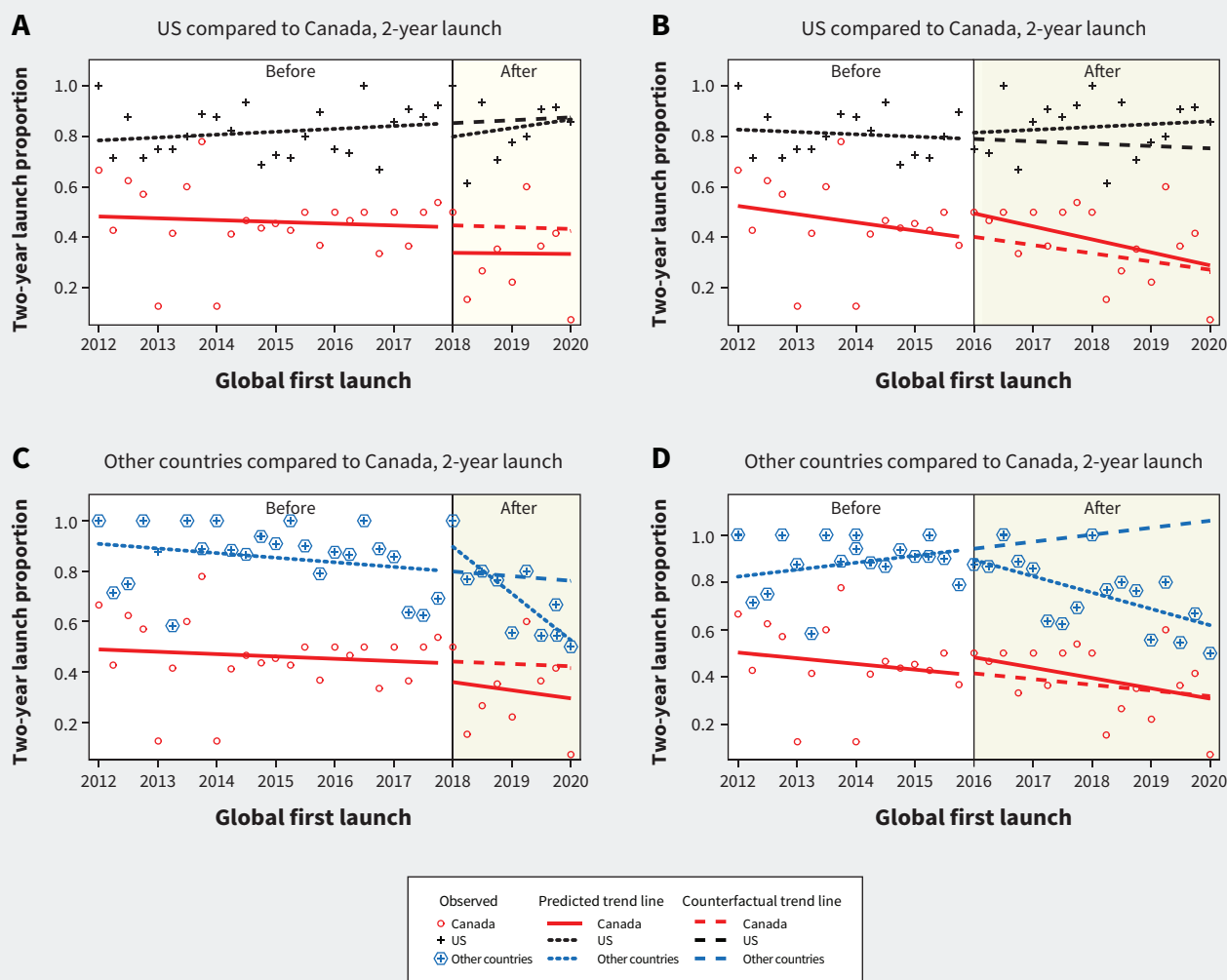
**Table 1: Characteristics of molecules included for 2-year launch**

| Variable                                                                                                           | No. (%) of molecules |                                                      |                                           |                                                      |                                           |
|--------------------------------------------------------------------------------------------------------------------|----------------------|------------------------------------------------------|-------------------------------------------|------------------------------------------------------|-------------------------------------------|
|                                                                                                                    | Overall<br>n = 349   | Main analysis                                        |                                           | Sensitivity analysis                                 |                                           |
|                                                                                                                    |                      | Before uncertain<br>period<br>(2012–2017)<br>n = 242 | Uncertain period<br>after 2017<br>n = 107 | Before uncertain<br>period<br>(2012–2015)<br>n = 162 | Uncertain period<br>after 2015<br>n = 187 |
| No. of comparators in Canada*                                                                                      |                      |                                                      |                                           |                                                      |                                           |
| 0                                                                                                                  | 46 (13.2)            | 31 (12.8)                                            | 15 (14.0)                                 | 26 (16.0)                                            | 20 (10.7)                                 |
| 1–4                                                                                                                | 209 (59.9)           | 148 (61.2)                                           | 61 (57.0)                                 | 103 (63.6)                                           | 106 (56.7)                                |
| > 4                                                                                                                | 94 (26.9)            | 63 (26.0)                                            | 31 (29.0)                                 | 33 (20.4)                                            | 61 (32.6)                                 |
| High price (in the top 10%)                                                                                        |                      |                                                      |                                           |                                                      |                                           |
| Yes                                                                                                                | 91 (26.1)            | 67 (27.7)                                            | 24 (22.4)                                 | 43 (26.5)                                            | 48 (25.7)                                 |
| No                                                                                                                 | 258 (73.9)           | 175 (72.3)                                           | 83 (77.6)                                 | 119 (73.5)                                           | 139 (74.3)                                |
| First-year sales in the US                                                                                         |                      |                                                      |                                           |                                                      |                                           |
| > \$20 million                                                                                                     | 187 (53.6)           | 137 (56.6)                                           | 50 (46.7)                                 | 92 (56.8)                                            | 95 (50.8)                                 |
| ≤ \$20 million                                                                                                     | 162 (46.4)           | 105 (43.4)                                           | 57 (53.3)                                 | 70 (43.2)                                            | 92 (49.2)                                 |
| ATC classification first level                                                                                     |                      |                                                      |                                           |                                                      |                                           |
| B: Blood and blood forming organs                                                                                  | 22 (6.3)             | 12 (5.0)                                             | 10 (9.3)                                  | 8 (4.9)                                              | 14 (7.5)                                  |
| J: Antiinfectives for systemic use                                                                                 | 55 (15.8)            | 40 (16.5)                                            | 15 (14.0)                                 | 24 (14.8)                                            | 31 (16.6)                                 |
| L: Antineoplastic and immunomodulating agents                                                                      | 117 (33.5)           | 75 (31.0)                                            | 42 (39.3)                                 | 50 (30.9)                                            | 67 (35.8)                                 |
| N: Nervous system                                                                                                  | 28 (8.0)             | 15 (6.2)                                             | 13 (12.1)                                 | 8 (4.9)                                              | 20 (10.7)                                 |
| Other ATC                                                                                                          | 127 (36.4)           | 100 (41.3)                                           | 27 (25.2)                                 | 72 (44.4)                                            | 55 (29.4)                                 |
| A: Alimentary tract and metabolism                                                                                 | 53 (15.2)            | 48 (19.8)                                            | 5 (4.7)                                   | 35 (21.6)                                            | 18 (9.6)                                  |
| C: Cardiovascular system                                                                                           | 11 (3.2)             | 8 (3.3)                                              | 3 (2.8)                                   | 8 (4.9)                                              | 3 (1.6)                                   |
| D: Dermatologicals                                                                                                 | 10 (2.9)             | 8 (3.3)                                              | 2 (1.9)                                   | 4 (2.5)                                              | 6 (3.2)                                   |
| G: Genito urinary system and sex hormones                                                                          | 4 (1.1)              | 2 (0.8)                                              | 2 (1.9)                                   | 2 (1.2)                                              | 2 (1.1)                                   |
| H: Systemic hormonal preparations, excluding sex hormones and insulins                                             | 5 (1.4)              | 3 (1.2)                                              | 2 (1.9)                                   | 1 (0.6)                                              | 4 (2.1)                                   |
| M: Musculo-skeletal system                                                                                         | 10 (2.9)             | 6 (2.5)                                              | 4 (3.7)                                   | 2 (1.2)                                              | 8 (4.3)                                   |
| P: Antiparasitic products, insecticides and repellents                                                             | 1 (0.3)              |                                                      | 1 (0.9)                                   |                                                      | 1 (0.5)                                   |
| R: Respiratory system                                                                                              | 17 (4.9)             | 14 (5.8)                                             | 3 (2.8)                                   | 11 (6.8)                                             | 6 (3.2)                                   |
| S: Sensory organs                                                                                                  | 8 (2.3)              | 4 (1.7)                                              | 4 (3.7)                                   | 2 (1.2)                                              | 6 (3.2)                                   |
| V: Various                                                                                                         | 8 (2.3)              | 7 (2.9)                                              | 1 (0.9)                                   | 7 (4.3)                                              | 1 (0.5)                                   |
| Note: ATC = Anatomical Therapeutic Chemical.                                                                       |                      |                                                      |                                           |                                                      |                                           |
| *The molecules in the same ATC fourth level that were sold in Canada in the quarter after the global first launch. |                      |                                                      |                                           |                                                      |                                           |

uncertain period was  $-0.81$  (SE 0.40;  $p = 0.045$ ) for the subgroup with price not in the top 10% and  $-1.07$  (SE 0.45;  $p = 0.02$ ) for the subgroup with first-year US sales greater than \$20 million, suggesting that the decrease of the log odds of launching these molecules in the other-countries group was greater than in Canada (Appendix 6, Table S7).

Compared with the 2-year launch analyses, the analysis of log odds of 1-year launching also suggested no detectable differences when comparing the US and the other-countries group with Canada (Table 2).

Appendix 6, Table S4 presents the logistic regression results for 2-year launch by comparing each specific country with Canada.



**Figure 2:** Observed and predicted quarterly 2-year launch proportion of new molecules in the United States (A and B) and other countries (C and D) compared with Canada. The period of uncertainty starts in 2018 in parts A and C and in 2016 in parts B and D. Two-year launch proportion indicates the proportion of new molecules launched in a specific country or a group of countries within 2 years of their global first launch. The other-countries group includes Australia, Belgium, France, Germany, Italy, Japan, the Netherlands, Norway, Spain, Sweden, Switzerland, and the United Kingdom. The counterfactual trend line is an extrapolation of the trend line before the uncertain period, representing what would have occurred had the policy uncertainty not happened.

The coefficients of the interaction terms suggested greater decreases in Norway ( $-0.69$ , SE  $0.31$ ;  $p = 0.03$ ) and Sweden ( $-0.63$ , SE  $0.29$ ;  $p = 0.03$ ) than in Canada. The findings from main and sensitivity analyses comparing the US and the other-countries group with Canada are summarized in Table 4.

## Interpretation

All analyses showed similar changes or even greater decreases in 2-year or 1-year launch after policy-uncertainty effective date in the other 12 comparator countries as a whole and in Norway and Sweden, compared with Canada. Almost all analyses showed similar changes in launches in the US and Canada. These findings suggest no important negative impact on launch from the policy uncertainty in Canada.

However, an exception was observed among new molecules with major benefit. When we used our main analytic approach,

the 2-year launch proportion appeared to decrease substantially in both Canada and the other-countries group after the 2017 effective date but increased in the US. The logistic regression results also suggested a detectable difference in launches comparing Canada and the US, using 2015 as the effective date. Despite these observed differences, we were unable to test the difference statistically using logistic regression when we used 2017 as the effective date, because of the 100% launch proportion in the US after 2017.

The observed potential early impact of the policy uncertainty on the 2-year launch for molecules with major benefit in our study mainly depended on the country with which Canada was compared. The US is no longer considered as a comparator country by PMPRB because it does not have effective policies to constrain medicine prices.<sup>13</sup> We chose to include the US as a comparator because patients and health care providers in Canada are more likely to be aware of the availability of new medicines in the US

**Table 2: The impact of the uncertain-policy period on log odds of launching in the United States and other countries compared with Canada in main and sensitivity analyses**

| Model parameters* (models in which December 2017 was used as the effective date) | Two-year launch     |         |                     |         | One-year launch     |         |                     |         |
|----------------------------------------------------------------------------------|---------------------|---------|---------------------|---------|---------------------|---------|---------------------|---------|
|                                                                                  | US                  |         | Other countries     |         | US                  |         | Others countries    |         |
|                                                                                  | Coefficient<br>± SE | p value | Coefficient<br>± SE | p value | Coefficient<br>± SE | p value | Coefficient<br>± SE | p value |
| Uncertain period after 2017                                                      | -0.59 ± 0.30        | 0.05    | -0.48 ± 0.26        | 0.06    | -0.04 ± 0.28        | 0.9     | -0.10 ± 0.25        | 0.7     |
| Before uncertain period (2012–2017)                                              | Ref.                |         | Ref.                |         | Ref.                |         | Ref.                |         |
| Comparison country                                                               | 2.29 ± 0.22         | < 0.001 | 2.21 ± 0.23         | < 0.001 | 2.91 ± 0.24         | < 0.001 | 2.29 ± 0.19         | < 0.001 |
| Canada                                                                           | Ref.                |         | Ref.                |         | Ref.                |         | Ref.                |         |
| Comparison country × Uncertain period†                                           | 0.75 ± 0.42         | 0.08    | -0.28 ± 0.36        | 0.4     | 0.47 ± 0.37         | 0.2     | -0.29 ± 0.31        | 0.4     |
| Comparison country × Before uncertain period†                                    | Ref.                |         | Ref.                |         | Ref.                |         | Ref.                |         |

| Model parameters* (models in which December 2015 was used as the effective date) | Two-year launch     |         |                     |         | One-year launch     |         |                     |         |
|----------------------------------------------------------------------------------|---------------------|---------|---------------------|---------|---------------------|---------|---------------------|---------|
|                                                                                  | US                  |         | Other countries     |         | US                  |         | Others countries    |         |
|                                                                                  | Coefficient<br>± SE | p value | Coefficient<br>± SE | p value | Coefficient<br>± SE | p value | Coefficient<br>± SE | p value |
| Uncertain period after 2015                                                      | -0.30 ± 0.27        | 0.3     | -0.20 ± 0.23        | 0.4     | -0.02 ± 0.26        | 0.9     | -0.04 ± 0.24        | 0.9     |
| Before uncertain period (2012–2015)                                              | Ref.                |         | Ref.                |         | Ref.                |         | Ref.                |         |
| Comparison country                                                               | 2.26 ± 0.27         | < 0.001 | 2.45 ± 0.28         | < 0.001 | 2.84 ± 0.28         | < 0.001 | 2.41 ± 0.25         | < 0.001 |
| Canada                                                                           | Ref.                |         | Ref.                |         | Ref.                |         | Ref.                |         |
| Comparison country × Uncertain period†                                           | 0.49 ± 0.36         | 0.2     | -0.59 ± 0.35        | 0.09    | 0.43 ± 0.35         | 0.2     | -0.39 ± 0.31        | 0.2     |
| Comparison country × Before uncertain period†                                    | Ref.                |         | Ref.                |         | Ref.                |         | Ref.                |         |

Note: Other countries = Australia, Belgium, France, Germany, Italy, Japan, the Netherlands, Norway, Spain, Sweden, Switzerland, and the United Kingdom; Ref. = reference category; SE = standard error.

\*Generalized estimating equation logistic regression adjusted for the first level of Anatomical Therapeutic Chemical, number of comparators in Canada, high price, and first-year sales in the US. The first row indicates the difference in log odds of launching between the uncertain period and before the uncertain period in Canada; the third row indicates the difference in log odds of launching between the comparison country and Canada before the uncertain period; the fifth row indicates the difference between the change of the log odds of launching during the uncertain period (v. before) in the comparison country and that in Canada.

†The multiplication sign indicates an interaction term.

(v. in other countries) and may wonder why certain medicines are available in the US but not in Canada.

Only Lexchin has compared the launching trend in Canada with another country and assessed the therapeutic value of the molecules that were not launched in Canada.<sup>6,36</sup> One of these studies found that the annual proportion of submissions to Health Canada among the drugs approved by the US FDA decreased from 2014 to 2021 but that this decrease was not different before and after 2017.<sup>36</sup> However, Lexchin did not compare the change before and after the publication of the proposed amendments in Canada with the change in other countries.<sup>36</sup> A separate study showed the same declining trend in Australia from 2011 to 2020 but did not compare the difference before and after 2017.<sup>6</sup>

Compared with previous studies, we found a greater number of medicines with major or moderate benefit that were not launched in Canada, during a similar period. Among the 117 medicines that

were not launched in Canada after 2015 (i.e., 2016–2021) in our study, 18 were rated as having major benefit and 5 as moderate benefit. Gaudette and colleagues found only 1 medicine with non-quantifiable added benefit, which was considered as little to no benefit in our study, out of 75 medicines that were not submitted to Health Canada from 2016 to February 2023.<sup>5</sup> Of 116 medicines not submitted to Health Canada in 2014–2021, Lexchin found 4 with major benefit and 2 with moderate benefit.<sup>36</sup> These differences could be attributed to different therapeutic rating approaches: IQWiG used by Gaudette and colleagues; IQWiG and *Prescrire International* used by Lexchin; and PMPRB, IQWiG, *Prescrire International* and FDA breakthrough therapy designation (if required) used in our study. Both previous studies focused on medicines approved by the FDA or the European Medicines Agency (EMA). We chose to use the first sale date to define the launch consistently across the 14 countries using IQVIA MIDAS data, which reflected the timing and speed of both approval and actual marketing. Furthermore,

**Table 3: Number and proportion of new molecules launched within 2 years of their global first launch by country, policy period, and therapeutic benefit**

| Therapeutic benefit rating*                                                                                                                                                                                                                                                                                                                                                         | No. (%)                                        |            |            |                 |                                        |           |            |                 |                  |         |                            |         |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|------------|------------|-----------------|----------------------------------------|-----------|------------|-----------------|------------------|---------|----------------------------|---------|
|                                                                                                                                                                                                                                                                                                                                                                                     | Before uncertain period (2012–2017)<br>n = 242 |            |            |                 | Uncertain period after 2017<br>n = 107 |           |            |                 | US v. Canada†    |         | Other countries v. Canada† |         |
|                                                                                                                                                                                                                                                                                                                                                                                     | Total                                          | Canada     | US         | Other countries | Total                                  | Canada    | US         | Other countries | US v. Canada†    |         | Other countries v. Canada† |         |
|                                                                                                                                                                                                                                                                                                                                                                                     |                                                |            |            |                 |                                        |           |            |                 | Coefficient ± SE | p value | Coefficient ± SE           | p value |
| Overall                                                                                                                                                                                                                                                                                                                                                                             | 242                                            | 109 (45.0) | 197 (81.4) | 203 (83.9)      | 107                                    | 33 (30.8) | 88 (82.2)  | 75 (70.1)       | 0.75 ± 0.42      | 0.08    | −0.28 ± 0.36               | 0.4     |
| Major                                                                                                                                                                                                                                                                                                                                                                               | 24                                             | 11 (45.8)  | 22 (91.7)  | 21 (87.5)       | 16                                     | 5 (31.3)  | 16 (100)   | 10 (62.5)       | NA               | NA      | −0.88 ± 1.24               | 0.5     |
| Moderate                                                                                                                                                                                                                                                                                                                                                                            | 45                                             | 34 (75.6)  | 42 (93.3)  | 44 (97.8)       | 12                                     | 8 (66.7)  | 10 (83.3)  | 11 (91.7)       | NA               | NA      | NA                         | NA      |
| Little to no                                                                                                                                                                                                                                                                                                                                                                        | 107                                            | 60 (56.1)  | 95 (88.8)  | 96 (89.7)       | 40                                     | 20 (50)   | 40 (100)   | 33 (82.5)       | NA               | NA      | −0.48 ± 0.70               | 0.5     |
| Missing rating                                                                                                                                                                                                                                                                                                                                                                      | 66                                             | 4 (6.1)    | 38 (57.6)  | 42 (63.6)       | 39                                     | 0 (0)     | 22 (56.4)  | 21 (53.8)       | NA               | NA      | NA                         | NA      |
|                                                                                                                                                                                                                                                                                                                                                                                     |                                                |            |            |                 |                                        |           |            |                 |                  |         |                            |         |
| Therapeutic benefit rating*                                                                                                                                                                                                                                                                                                                                                         | Before uncertain period (2012–2015)<br>n = 162 |            |            |                 | Uncertain period after 2015<br>n = 187 |           |            |                 | US v. Canada†    |         | Other countries v. Canada† |         |
|                                                                                                                                                                                                                                                                                                                                                                                     | Total                                          | Canada     | US         | Other countries | Total                                  | Canada    | US         | Other countries | Coefficient ± SE | p value | Coefficient ± SE           | p value |
| Overall                                                                                                                                                                                                                                                                                                                                                                             | 162                                            | 72 (44.4)  | 131 (80.9) | 140 (86.4)      | 187                                    | 70 (37.4) | 154 (82.4) | 138 (73.8)      | 0.49 ± 0.36      | 0.2     | −0.59 ± 0.35               | 0.09    |
| Major                                                                                                                                                                                                                                                                                                                                                                               | 13                                             | 7 (53.8)   | 12 (92.3)  | 13 (100)        | 27                                     | 9 (33.3)  | 26 (96.3)  | 18 (66.7)       | 3.79 ± 1.66      | 0.02    | NA                         | NA      |
| Moderate                                                                                                                                                                                                                                                                                                                                                                            | 34                                             | 24 (70.6)  | 32 (94.1)  | 33 (97.1)       | 23                                     | 18 (78.3) | 20 (87.0)  | 22 (95.7)       | NA               | NA      | NA                         | NA      |
| Little to no                                                                                                                                                                                                                                                                                                                                                                        | 71                                             | 39 (54.9)  | 63 (88.7)  | 63 (88.7)       | 76                                     | 41 (53.9) | 72 (94.7)  | 66 (86.8)       | 1.17 ± 0.73      | 0.1     | −0.09 ± 0.65               | 0.9     |
| Missing rating                                                                                                                                                                                                                                                                                                                                                                      | 44                                             | 2 (4.5)    | 24 (54.5)  | 31 (70.5)       | 61                                     | 2 (3.3)   | 36 (59.0)  | 32 (52.5)       | −0.42 ± 1.19     | 0.7     | −0.51 ± 1.17               | 0.7     |
|                                                                                                                                                                                                                                                                                                                                                                                     |                                                |            |            |                 |                                        |           |            |                 |                  |         |                            |         |
| Note: NA = not applicable (regressions could not be estimated owing to small samples and sparseness), SE = standard error.                                                                                                                                                                                                                                                          |                                                |            |            |                 |                                        |           |            |                 |                  |         |                            |         |
| *First based on the highest rating from the Patented Medicine Prices Review Board, the Institute for Quality and Efficiency in Health Care in Germany, and the independent French medicine bulletin <i>Prescrire International</i> , and then the breakthrough therapy designation by the Center for Drug Evaluation and Research of the US Food and Drug Administration.           |                                                |            |            |                 |                                        |           |            |                 |                  |         |                            |         |
| †Coefficient and standard error for the interaction term in the generalized estimating equation logistic regression, including uncertain period, comparison country, and interaction between uncertain period and comparison country, adjusted for the first level of Anatomical Therapeutic Chemical, number of comparators in Canada, high price, and first-year sales in the US. |                                                |            |            |                 |                                        |           |            |                 |                  |         |                            |         |

we compared the proportion of medicines launched in Canada with the US and other countries by therapeutic benefit ratings, which was not done in the previous studies.

Limitations

One limitation of our study is that we did not assess time to launch or launch lag because of the short observation periods. Instead, we assessed the launches in Canada within 2 years and 1 year of global first launch, a coarser measure of the launch speed. We also could not conduct some subgroup analyses because of the small number of launches or nonlaunches in each subgroup and in some individual countries.

Samples were small, particularly in subgroup analyses, which may have decreased our ability to detect an impact of the policy uncertainty. The many subgroup analyses conducted increased the likelihood that some of the differences we found might have been due to chance. Had we used a significance level of a *p* value less than 0.1, logistic regression results would have suggested that the decrease in 2-year launch in Canada tended to be greater than in the US and France among all samples, and in the US among the subgroups with nervous system ATC, 1–4 or more than 4 comparators, price not in the top 10%, first-year US sales \$20 million or lower, or drugs that conferred little to no benefit (Appendix 6, Table S10). The decrease in 2-year launch in Canada might be smaller than in the other 12 countries as a group.

Our results could be affected by unobserved or unmeasured factors. The COVID-19 pandemic may have had an impact on the launch decision or submission for market approval by pharmaceutical companies, market approval time by regulatory agencies, and time from market approval to sales,<sup>59</sup> which could be associated with fewer launches. It is also possible that in an effort to dissuade the government or PMPRB from following through with the proposed regulatory amendments, industry followed through on its claim<sup>6,60,61</sup> and did not launch medicines in Canada, which might lead to the observed reduction in launches during our study period. Furthermore, some policies or changes in the comparator countries could have affected their drug launches. For example, the implemented *21st Century Cures Act* in December 2016 enables the US FDA to modernize clinical trial designs including the use of real-world evidence, which could speed the review of novel medical products.<sup>62</sup> The share of orphan drugs among new approvals by the US FDA, EMA, or Health Canada increased from an average of 33% in 2009–2014<sup>43</sup> to 47% in 2016–2021.<sup>44</sup> Special health technology assessment or reimbursement considerations are applied for orphan drugs in some countries such as Canada, Germany, the Netherlands, Sweden, and the UK.<sup>63–65</sup> The Netherlands implemented a “lock” system in 2015 that could postpone the reimbursement of new medicines with disproportionately high costs per treatment or a high budget impact.<sup>66</sup> To minimize the potential confounding effect, we applied a quasi-experimental design using the US and other countries as the comparison group. However, our

**Table 4: Result summary by uncertain period, comparison country, and analysis method**

| Analysis                                        | Uncertain period after 2017 |                 | Uncertain period after 2015 |                         |
|-------------------------------------------------|-----------------------------|-----------------|-----------------------------|-------------------------|
|                                                 | US                          | Other countries | US                          | Other countries         |
| Interrupted time series: 2-year launch*         | No                          | No              | No                          | No                      |
| GEE logistic regression: 2-year launch†         | No                          | No              | No                          | No                      |
| Subgroups: 2-year launch†                       |                             |                 |                             |                         |
| ATC: Blood and blood forming organs             | NA                          | No              | NA                          | NA                      |
| ATC: Antiinfectives for systemic use            | No                          | No              | No                          | No                      |
| ATC: Antineoplastic and immunomodulating agents | No                          | No              | No                          | No                      |
| ATC: nervous system                             | No                          | No              | No                          | No                      |
| Other ATC                                       | No                          | No              | No                          | No                      |
| No. of comparators: 0                           | No                          | No              | No                          | No                      |
| No. of comparators: 1–4                         | No                          | No              | No                          | No                      |
| No. of comparators: > 4                         | No                          | No              | No                          | No                      |
| High price in the top 10%                       | No                          | No              | No                          | No                      |
| Price not in the top 10%                        | No                          | No              | No                          | More launches in Canada |
| First-year sales in US > \$20 million           | No                          | No              | No                          | More launches in Canada |
| First-year sales in US ≤ \$20 million           | No                          | No              | No                          | No                      |
| Major therapeutic benefit                       | NA                          | No              | Fewer launches in Canada    | NA                      |
| Moderate therapeutic benefit                    | NA                          | NA              | NA                          | NA                      |
| Little to no therapeutic benefit                | NA                          | No              | No                          | No                      |
| Imputed therapeutic benefit rating‡             |                             |                 |                             |                         |
| Major therapeutic benefit                       | No                          | No              | No                          | No                      |
| Moderate therapeutic benefit                    | No                          | NA              | No                          | NA                      |
| Little to no therapeutic benefit                | NA                          | No              | No                          | No                      |
| GEE logistic regression: 1-year launch†         | No                          | No              | No                          | No                      |

Note: ATC = Anatomical Therapeutic Chemical; GEE logistic regression = generalized estimating equation logistic regression adjusted for the first level of ATC, number of comparators in Canada, high price, and first-year sales in the US; NA = not applicable (regressions could not be estimated owing to small samples and sparseness); No = no detectable difference between Canada and the comparison countries.

\*Based on the 95% confidence interval of the difference between expected absolute changes over policy periods in Canada and the comparison country.

†Based on  $p$  value < 0.05 for the coefficient of the interaction term of comparison country and uncertain period in the GEE logistic regression; fewer launches: the decrease of the log odds of launching in Canada was larger; more launches: the decrease of the log odds of launching in Canada was smaller.

‡Further imputed by the designation of first-in-class and priority review by the US Food and Drug Administration.

estimates could be biased if the impact of the COVID-19 pandemic or other unmeasured confounders differed by country.

## Conclusion

The PMPRB's regulatory amendment process created a period during which pricing policies in Canada were highly uncertain. No negative impact of this uncertainty on new patented medicine launches in Canada was observed when comparing Canada with all other countries, except for medicines with major therapeutic benefit. The observed reduction in launch proportion for new medicines with major therapeutic benefit in Canada and other countries but not in the US requires close monitoring and further investigation.

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