CHPI Canadian Health Policy Institute

Annual Report

Waiting for new medicines in Canada, Europe and the United States 2016-2021

Waiting for new medicines in Canada, Europe and the United States 2016-2021

CONTRIBUTORS

(Alphabetical order)

Mark Rovere, PhD candidate, Canadian Health Policy Institute (CHPI)
Brett Skinner, PhD, Canadian Health Policy Institute (CHPI)

ATTRIBUTION

This paper is corporately authored and edited based on proprietary template models and methods that are intended to facilitate regular updates. The design and content are a cumulative reflection of the diverse contributions collectively attributable to the CHPI affiliated researchers who may have variously participated in updating each edition. Data sources, methods and editorial presentation may evolve from previous editions.

DISCLAIMER

This study uses data from IQVIA Inc. The analysis, conclusions and opinions expressed in this paper do not necessarily reflect the views of the data supplier.

CITATION

Canadian Health Policy Institute (CHPI) (2022). Waiting for new medicines in Canada, Europe and the United States 2016-2021. *Canadian Health Policy*, APR 2022. ISSN 2562-9492 https://doi.org/10.54194/SPOS4023 canadianhealthpolicy.com.

Table of Contents

HIGHLIGHTS

- The study compared the availability and wait for new medicines in Canada, the European Union and the United States. It examined new drug launches, regulatory approvals, and insurance coverage during the years 2016-2021.
- Canada was a low priority market for new drug launches relative to Europe and the United States. Health Canada received 205 applications for marketing authorization of drugs classified as new active substances, compared to 300 received by the European Medicines Agency (EMA) and 333 received by the US Food and Drug Administration (FDA). Pharmaceutical companies waited an average of 687 days after submitting the first new drug application to the EMA or the FDA to file an application for the same drug to Health Canada.
- Only half of the 350 new drugs that were approved by at least one of the regulators in the EU, US, and Canada were eventually available to Canadians. Health Canada reported 182 marketing authorizations for new drugs, while the FDA accrued 277 new drugs approved and the EMA accrued 208 new drugs approved. Comparing only the drugs approved in all jurisdictions, Health Canada took the longest average time to approve (358 days), followed by the EMA (301 days), while the FDA took the shortest time (270 days).
- Of the 350 new medicines authorized for marketing in at least one of the three jurisdictions during the study period, publicly insured Americans had access to 277, Germans had publicly insured access to 208, and publicly insured Canadians had access to only 43. The insurance coverage delay ranged from 724 days in Canada, to zero days in Germany and less than 180 days in the US.
- From the first global new drug application to formulary listing in a public drug plan, on average publicly insured Canadians waited up to 3.8 years longer than Americans insured under Medicare to get access to a new medicine under their drug plan, and almost 3.6 years longer than publicly insured Germans to get access to a new medicine under their drug plan.
- Patent term restoration should be extended to compensate for all time lost due to government regulations and processes. Canada's PTR currently compensates for a maximum two years lost patent time attributable to Health Canada's approval process. PTR does not compensate for subsequent delays caused by HTA, and federal-provincial formulary processes. Data showed that 87% of the new drugs covered under public drug plans, experienced waits from new drug application to formulary listing, exceeding the two-year (730 days) limit for PTR. The maximum wait was 2,457 days (6.7 years) and the average wait was 1,215 days (3.3 years).
- The availability and wait for new drugs could be improved through regulatory harmonization under which, Health Canada would automatically and immediately recognize new drug approvals occurring first in either the EMA or the FDA. Regulatory harmonization could have potentially made an additional 168 new drugs available to Canadians and shortened wait times by up to 610 days.
- Germany's system for pharmaceutical pricing and reimbursement, uses structured negotiation instead of regulation and is designed to allow immediate interim insurance coverage following marketing authorization, with permanent insurance coverage pending the outcome of negotiations. Expediting formulary listings using a similar approach in Canada would have shortened wait times by 724 days.

INTRODUCTION

Pathway to Access a New Drug in Canada

It takes a long time to successfully develop a new drug that will prove safe and effective for use by patients. A 2016 estimate based on the United States experience found that the time between the start of clinical testing of a novel drug molecule, and submission of a new drug application for marketing authorization was 80.8 months or 6.7 years. **[1]** However, the end of the research and development phase is just the beginning of the wait for access to new medicines caused by government policies affecting the geographic priority for new drug launches, regulatory approvals, and reimbursement processes.

Getting access to a successfully developed new drug under a public drug plan in Canada is a particularly complex and time-consuming bureaucratic process. Before a new drug can be sold in Canada, it must be authorized for marketing by the federal regulatory agency Health Canada, which reviews the clinical evidence to assess and certify the safety and therapeutic effectiveness of the product.

The prices of new medicines are also federally regulated by a quasi-judicial agency known as the Patented Medicine Prices Review Board (PMPRB). PMPRB reviews the clinical evidence to determine the applicability of price control guidelines and sets the ceiling price for new drugs using international, domestic, and therapeutic reference prices.

Further, new drugs are subject to health technology assessment (HTA) by the Canadian Agency for Drugs and Technology in Health (CADTH), which again reviews clinical evidence to assess the cost-effectiveness of the product and make recommendations regarding reimbursement on behalf of all federal and provincial public drug plans, except Quebec which utilizes its own HTA agency known as the Institut national d'excellence en santé et en services sociaux (INESSS).

Manufacturers of new drugs then enter price negotiation with the pan-Canadian Pharmaceutical Alliance (PCPA), which acts as a monopsony on behalf of every federal and provincial public drug plan. Under the direction of their respective Ministers of Health, public drug plans make the final decision about listing a new drug on the formulary, and the reimbursement price and conditions, within a budget allocated by the Minister.

This complex process determines the availability of new drugs, and how long Canadian patients must wait for insured access to new medicines. Despite its importance, policy makers have failed to scrutinize the impact of the process on access. Access to new medicines should be a higher priority for federal and provincial governments. A literature review published by CHPI in 2019, found 68 studies published in peer-reviewed academic journals from 1990 to 2018 affirming that greater use of innovative pharmaceuticals is empirically associated with improved patient and population health outcomes, reduced potential health system costs, and reduced societal costs like economic productivity losses from untreated or under-treated illness. **[2]** There is a lot to be gained from improving access to new drugs.

 | ISSN 2562-9492 | *Canadian Health Policy*, APR 2022

Objective

Inter-jurisdictional comparisons of access to new medicines can provide insights about the impact of policies and regulations, the performance of regulatory agencies, and the adequacy of insurance. This study compares the regulatory and reimbursement experience of new medicines in Canada, the European Union, and the United States. It introduces a novel accrual-based analysis to account for drugs matching Health Canada approvals during the years 2016-2020 that were approved in previous years in Europe or the United States. The analysis comprehensively examines the total wait time for insured access to new medicines, measured from the first global application for marketing authorization to inclusion on a public drug plan formulary.

METHOD

New medicines

A new medicine (i.e. innovative or patented, drug or pharmaceutical) was defined by the following criteria:

- Patented prescription drug product (chemical or biologic).
- Granted marketing authorization for human use in the European Union, the United States, and/or Canada, accruing during the calendar years 2016 to 2020.
- Categorized as a new active substance (NAS) by the European Medicines Agency (EMA) and/or Health Canada, or as a new molecular entity (NME) by the US Food and Drug Administration (FDA).

According to Health Canada, a new active substance is a new drug (pharmaceutical or biologic) that contains a medicinal ingredient not previously approved in a drug in Canada and that is not a variation of a previously approved medicinal ingredient. The EMA defines a new active substance as a drug not previously authorized as a medicinal product in the European Union. Similarly, the FDA defines a new molecular entity as an active ingredient that contains no active moiety that has been previously approved by the Agency or has been previously marketed as a drug in the United States.

The national availability of new medicines was estimated according to three criteria:

- New drug launches: the number of new drug applications submitted to each jurisdiction.
- Marketing authorizations: the number of regulatory approvals in each jurisdiction.
- Formulary listings: the number of new drugs covered under insurance in each jurisdiction.

New drug launches

This study uses the terminology “new drug application (NDA)” or “submissions” synonymously to include Health Canada’s “new drug submission (NDS)”; the FDA’s “new drug application (NDA)” and “biologic license application (BLA)”; and the EMA’s “marketing authorisation application (MAA)”. A new drug was deemed to be globally launched from the date of the first submission of a new drug application for marketing authorization to any of the EMA, the FDA, or Health Canada.

National launch was defined from the date of submission of a new drug application in each jurisdiction. The 'launch' definition used here differs from other analyses which define launch by the date of first sale. [3] CHPI's definition is based on the view that the NDA represents the earliest signal that the pharmaceutical manufacturer believes that its product is safe and effective and ready for use by patients. Thereafter, availability of the drug is determined by processes external to the manufacturer.

Accrued marketing authorizations

The study uses the terminology "marketing authorization (MA)" interchangeably with "regulatory approval(s)". Both terms mean that the national/central regulator has issued formal permission to sell a new drug. The study focused on new active substances authorized for marketing by Health Canada during the years 2016 to 2020. We used this group of drugs as a benchmark for comparison with marketing authorizations in the European Union and the United States during the same timeframe. Many of the new drugs approved by Health Canada during the study period, were approved by the FDA or the EMA in earlier years. Due to the Canadian focus of the study, products approved by the FDA or the EMA before January 1, 2016, were deemed to be accrued to the study period if they matched drugs approved by Health Canada during the study period. The comparative drugs from Europe and the United States were identified according to three criteria:

- New active substances (NAS) approved by the EMA and/or the FDA from 2016-2020 that were exact matches of NAS approved by Health Canada from 2016-2020.
- NAS approved by the EMA and/or the FDA before 2016 that were exact matches of NAS approved by Health Canada from 2016-2020 (i.e. accrued marketing authorizations).
- NAS approved by the EMA and/or the FDA from 2016-2020 that were different from the drugs approved by Health Canada from 2016-2020.

New drugs which met one of these three criteria were included in the study. The study excluded gene therapies and vaccines.

Insured access to new medicines

The study uses the terminology "formulary listings" interchangeably with "insurance coverage" or "reimbursement". Insured access to a new medicine was indicated by its inclusion on the formulary of a public drug plan. Insurance coverage was deemed to be the only meaningful concept of access because the cost of many pharmaceuticals would be financially unaffordable for most people without the risk pooling associated with private insurance plans or the subsidy associated with publicly funded drug plans.

The wait for insured access to new medicines was measured in three consecutive time segments:

- Launch priority delay: the number of days lapsed between the date that the first new drug application was submitted to any of the national pharmaceutical regulators in Canada, the European Union, or the United States, and the date that a new drug application for the same new active substance was submitted to the national regulator in each jurisdiction.

- Regulatory process delay: the number of days lapsed between the date that the new drug application was submitted within each jurisdiction, and the date of marketing authorization in each jurisdiction.
- Insurance coverage delay: the number of days lapsed between the date of marketing authorization, and the date that the medicine was included on an insurance formulary in the jurisdiction.

Calculations

The availability status was verified, and wait times metrics were calculated, for the same drug across all three national jurisdictions. For each jurisdiction, the aggregate number of new drug launches, marketing authorizations, and formulary listings were calculated from counts of dates posted in the database. The delays associated with launch priority, regulatory process, and insurance coverage were measured in days and were calculated by subtracting earlier dates from later dates marking the beginning and ending of the respective segment. For each jurisdiction wait times were averaged across all drugs identified for comparison during the study period. The federal–provincial formulary data were aggregated at the national level by jurisdictional population weighted average. The analysis does not account for the conditional status of the formulary listing (i.e. full benefit versus special authorization/ limited use/ exceptional access).

Data sources

The submission dates for new drug applications and the effective dates of regulatory approval were obtained by special request from Health Canada for all new active substances that were authorized for marketing from 1 January 2016 to 31 December 2020. **[APPENDIX EXHIBIT A]** Canadian formulary data were separately available for the 11 federal (Non-Insured Health Benefit NIHB) and provincial publicly funded drug plans from IQVIA Inc. **[**4**]** **[**5**]** The data were supplemented and cross-referenced by accessing the publicly available formulary lists from the federal and provincial drug plans and cancer care agencies. Formulary status was assessed current to 21 December 2021 to allow at least one year for formulary listings data to mature. Canadian population data were obtained from Statistics Canada. **[**6**]** The population of clients served under the NIHB were obtained from its most recent annual report. **[**7**]**

Comparable European and US data for new drug applications and regulatory approvals are published by the EMA and the FDA and available online. The EMA data covered the years 2000-2020, and the FDA data covered 1985-2020. **[**8**]** **[**9**]** Comparable data for the insurance coverage experience of new drugs in the EU and the US were not available.

The data were compiled into CHPI's Canadian Access to Innovative Medicines Database (CA2IMD). The database includes the brand name, generic name, manufacturer, jurisdictional regulator, submission class (e.g. NAS/NME), biologic/chemical identifier, new drug application date, marketing authorization date for drugs approved by the EMA, FDA, and Health Canada, and Canadian reimbursement data including first claim date across private sector drug plans, formulary listing dates for each federal and provincial drug plan, and the reimbursement status of each formulary listing. The database is updated annually.

RESULTS

Drugs Studied

In total, 350 unique new active substances met one of the three criteria for inclusion and were therefore defined as having received or accrued marketing authorization during the study period in at least one of the pharmaceutical regulators in Canada, the European Union, or the United States.

New Drug Launches

Each of the regulators publish aggregate data in their annual reports on the number of new drug applications for marketing authorization of new active substances received by the regulator. **EXHIBIT 1** shows the number of new drug applications received by the EMA, FDA, and Health Canada, during 2016-2020. During the study period, Health Canada received 205 submissions for marketing authorization, compared to 300 received by the EMA, and 333 by the FDA. The data indicate that Canada was a low priority market for new drug launches relative to the EU and the US.

Canada's status as a low priority market for new drug launches is also reflected by the infrequent occasions when Health Canada was first to receive a new drug application among the three national regulators. **EXHIBIT 2** shows number of cases in which each national regulator was first to receive a new drug application for marketing authorization of the 350 new active substances approved by at least one of the EMA, the FDA, and Health Canada accruing during 2016-2020.

The United States was the highest priority market for new drug launches among all three jurisdictions. Canada was the lowest priority market. Health Canada was the first to receive an NDA for only 22 of 350 NAS studied. The EMA was first to receive 89, and the FDA was first to receive 239.

The delay to access new medicines that is attributable to the geographic order of priority for launching a new drug product into global markets was measured from first new drug application in any jurisdiction, to the submission of a new drug application to each of the national regulators. **EXHIBIT 3** shows the average number of days between the first new drug application submitted among the EMA, the FDA and HC (aka "global launch") and submission of a new drug application to each domestic regulator (aka "national launch") for the same new active substance. This period represents the delay that is caused by launch prioritization.

Across the 350 drugs included in the study, pharmaceutical companies waited an average of 687 days after the first new drug application submission (EMA or FDA or HC) to file a new drug application for the same new active substance to Health Canada during the study period. The corresponding wait for national drug launch was 141 days for the EMA, and 98 days for the FDA.

EXHIBIT 1. Total new drug applications received 2016–2020

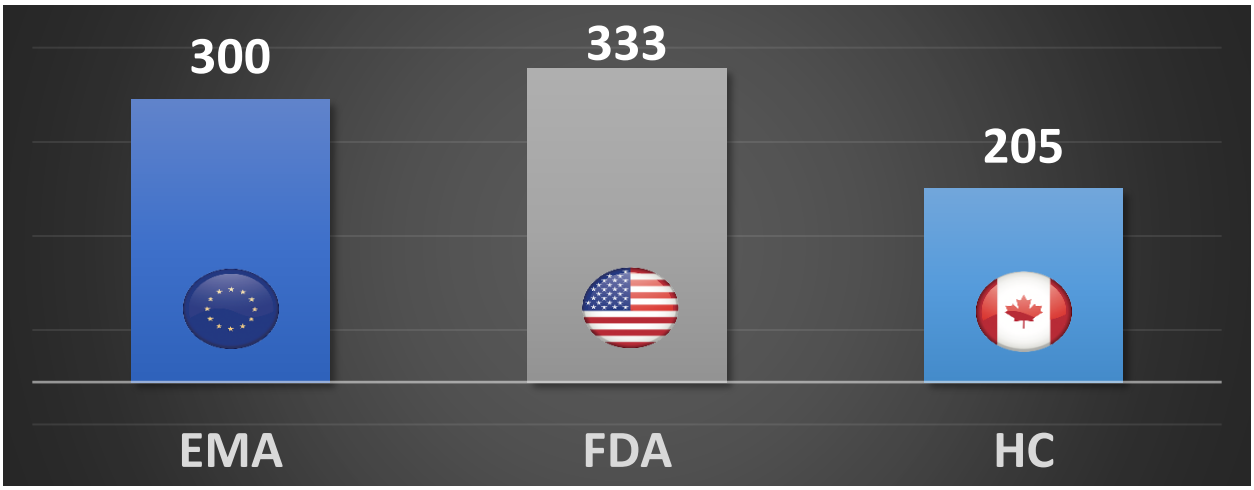


EXHIBIT 2. First market to receive a new drug application 2016-2020

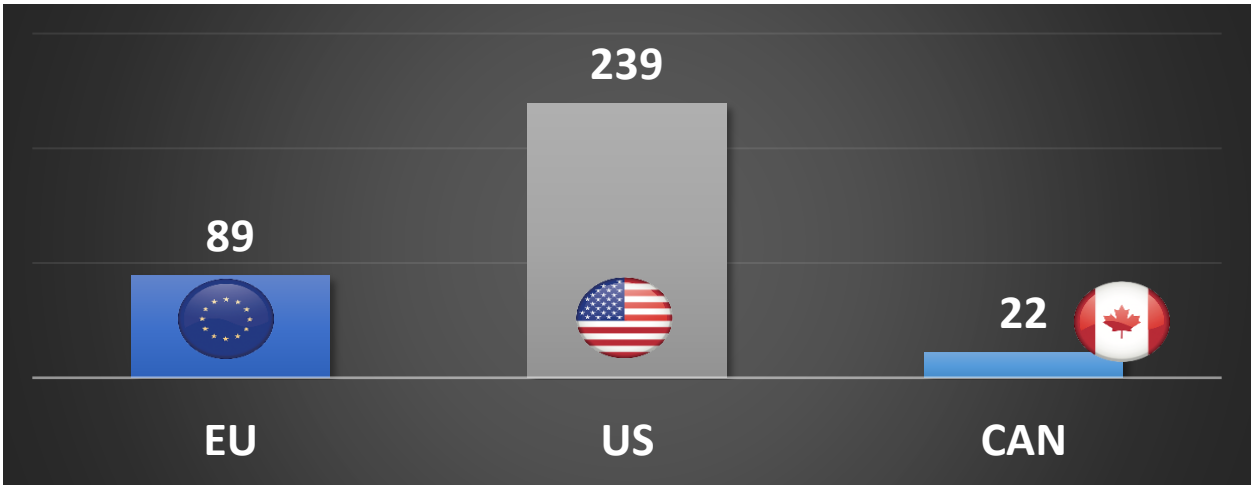
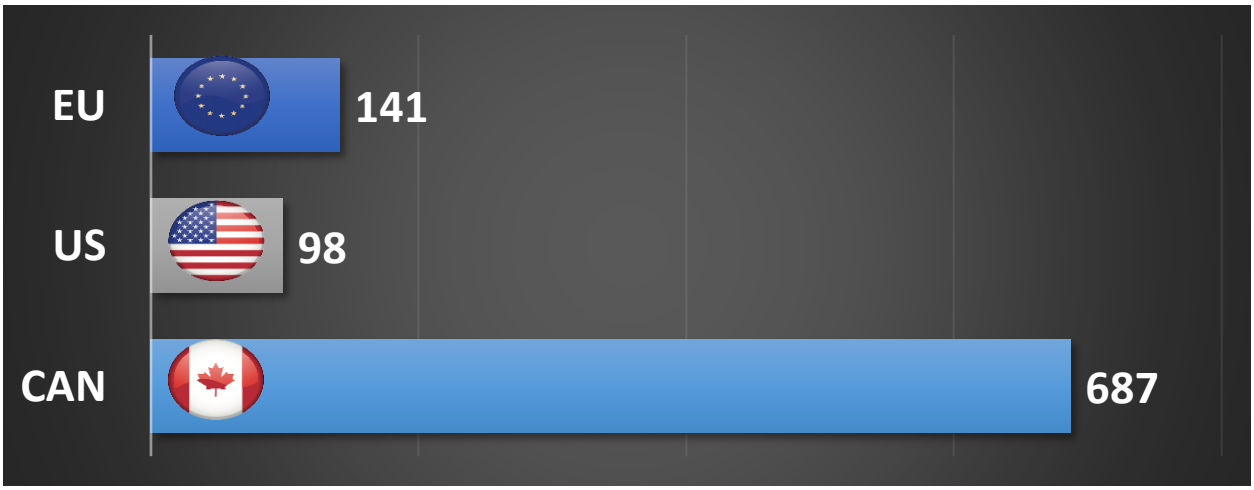


EXHIBIT 3. Wait time from first global NDA to national NDA for the same NAS



Marketing Authorizations

EXHIBIT 4 displays the number of marketing authorizations for new drugs issued or accruing during 2016 to 2020. Results are shown separately by national regulator. The comparison uses the group of drugs approved by Health Canada during the period as a benchmark and accounts for the accrued status of a new drug.

The bars are segmented to separately show the number of drugs authorized for marketing in common with Health Canada during 2016-2020, the number of unique drugs authorized for marketing during the same period, and the number of drugs in common with drugs approved by Health Canada during 2016–2020, but which accrued marketing authorization before 2016.

Health Canada reported 182 marketing authorizations for new active substances during 2016-2020 or 52% of the 350 new drugs accruing approval across all three regulators during 2016-2020. The FDA authorized 277 NAS or 79% of the total available, and the EMA authorized 208 or 59%.

Health Canada approved a higher percentage of the new drug applications submitted only to the agency (182 of 205 or 89%) than the EMA (208 of 300, 69%) or the FDA (277 of 333, 83%) did of the submissions they received. However, Health Canada approvals tend to occur after EMA/FDA approvals and submissions to Health Canada are mostly represented by products that have already been preapproved by the other jurisdictions.

The delay to access caused by the regulatory process is represented by the time between the date of the new drug application and the date of marketing authorization by the national regulator. **EXHIBIT 5** shows the average number of days from new drug application to national marketing authorization in the EMA, FDA, and Health Canada. Results are shown only for accrued marketing authorizations for the new active substances that were in common with the NAS approved by Health Canada.

Health Canada took 358 days on average to approve a new active substance. The EMA took 301 days, and the FDA took 270 days to authorize the same drugs.

EXHIBIT 4. Accrued marketing authorizations issued for new drugs 2016–2020

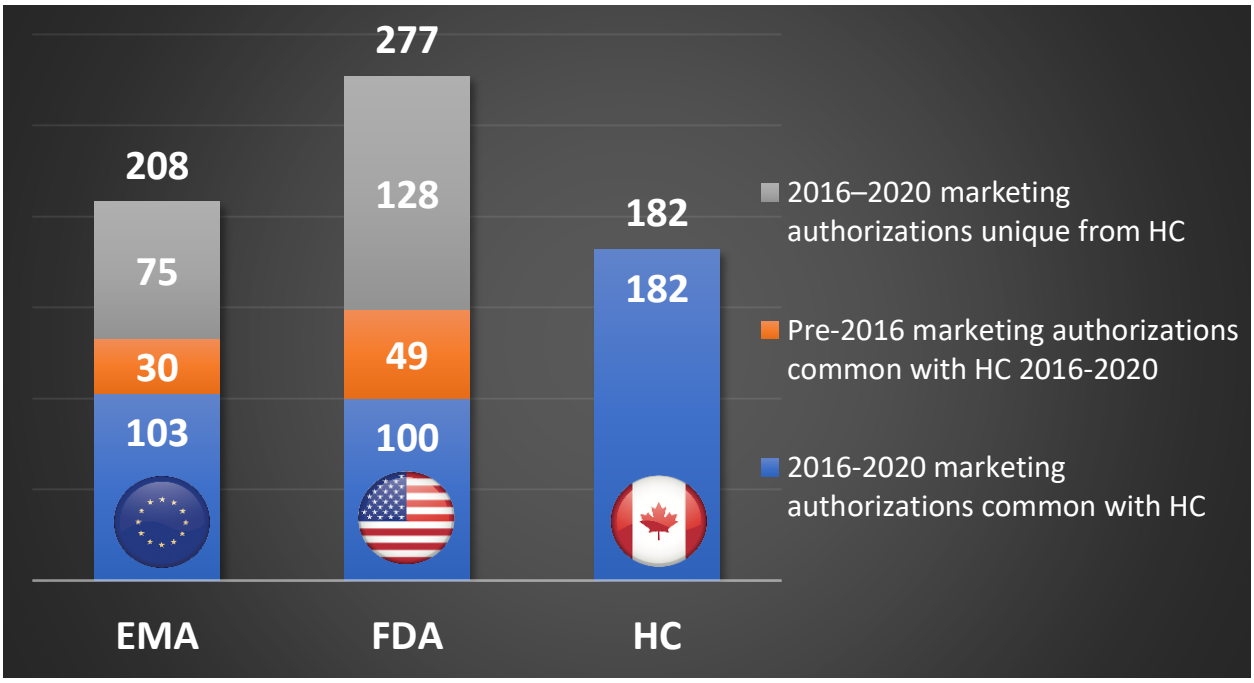
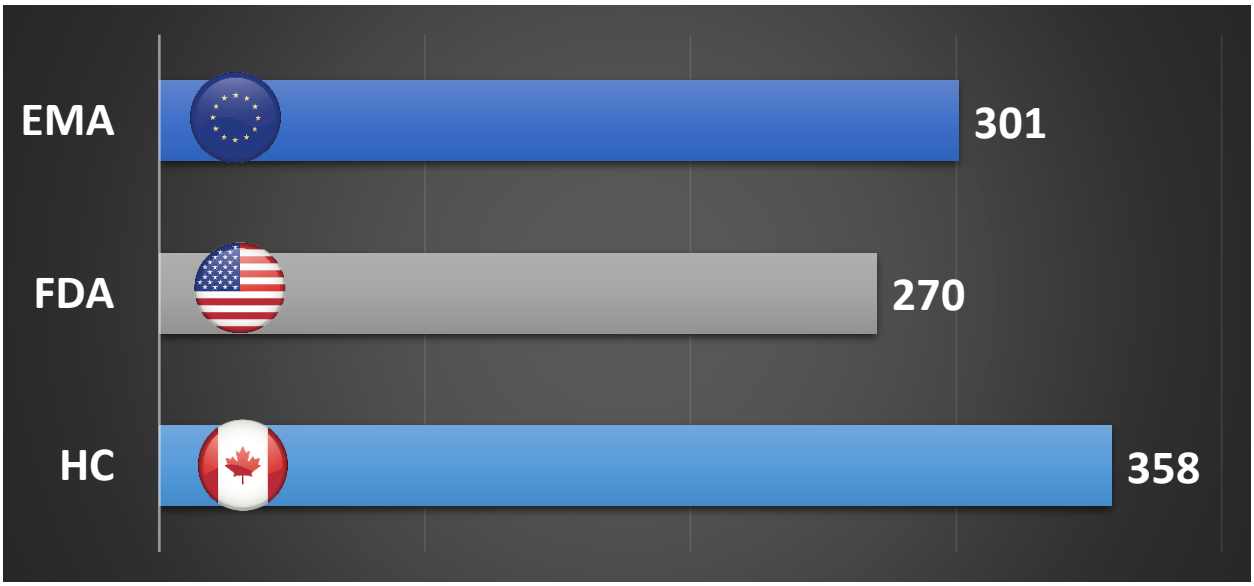


EXHIBIT 5. Average number of days between NDA and marketing authorization for all accrued approvals in common with Health Canada 2016–2020



Formulary Listings

Comparison of publicly funded drug insurance in Canada, the European Union and the United States was limited by data availability and complicated by differences in the structure of each system. Formulary listing data were available only for Canada. However, we were able to compare across jurisdictions by applying some general assumptions based on the structure of pricing and reimbursement in publicly funded drug plans in the Europe and Medicare Part D in the United States.

In Canada, provincial governments offer publicly funded drug benefits to seniors and low-income households, with special programs for particular diseases. The federal government offers public benefits to the aboriginal population. About 1/3 of the population is eligible under these programs. In addition, provincial governments are the universal payer of last resort for people who incur uninsured out-of-pocket costs exceeding income-based deductibles.

In Europe, marketing authorization is centralized, but prescription drug insurance is the responsibility of the national entities of the EU. Germany is not generally representative of the European situation but is presented here as an example. In Germany, publicly funded drug benefits are provided through the statutory health insurance funds, and beneficiaries are exposed to deductibles and copayments. Due to the structure of public drug reimbursement in Germany (explained later in this paper, see “Expedited formulary listing”), new medicines are added to public formularies immediately following EMA marketing authorization.

In the United States publicly subsidized drug benefits are provided through Medicare Part D, which is financed from general revenues (73%), beneficiary premiums (15%), and state contributions (11%). Medicare Part D drug plan sponsors must review new drugs and decide on coverage within 180 days of FDA approval. Formularies must include at least two chemically distinct drugs for each therapeutic class, and any additional drugs presenting therapeutic advantages. **[10]** Part D plan sponsors typically list all NAS drugs on formulary and adjust the level of insurance coverage by tiered premiums, deductibles and copayments.

We assumed that German public drug plans cover all NAS approved by the EMA immediately, and that US Medicare Part D drug plans covered all NAS approved by the FDA within six months. Based on these assumptions and the available data, on average Germans had publicly insured access to 208 of the 350 new medicines authorized for marketing in at least one of the three jurisdictions during the study period, publicly insured Americans had access to 277 new medicines, and publicly insured Canadians had access to only 43 new medicines. [**EXHIBIT 6**] The insurance coverage delay is represented by the time between the date of national marketing authorization and inclusion on a publicly funded drug plan formulary. **EXHIBIT 7** shows the average number of days from national marketing authorization to public formulary listing in each jurisdiction. The data indicate that the insurance coverage delay, ranged from 724 days in Canada, to zero days in Germany and between zero and a maximum of 180 days in the US.

EXHIBIT 6. Count of new medicines covered under public drug plans 2016-2021

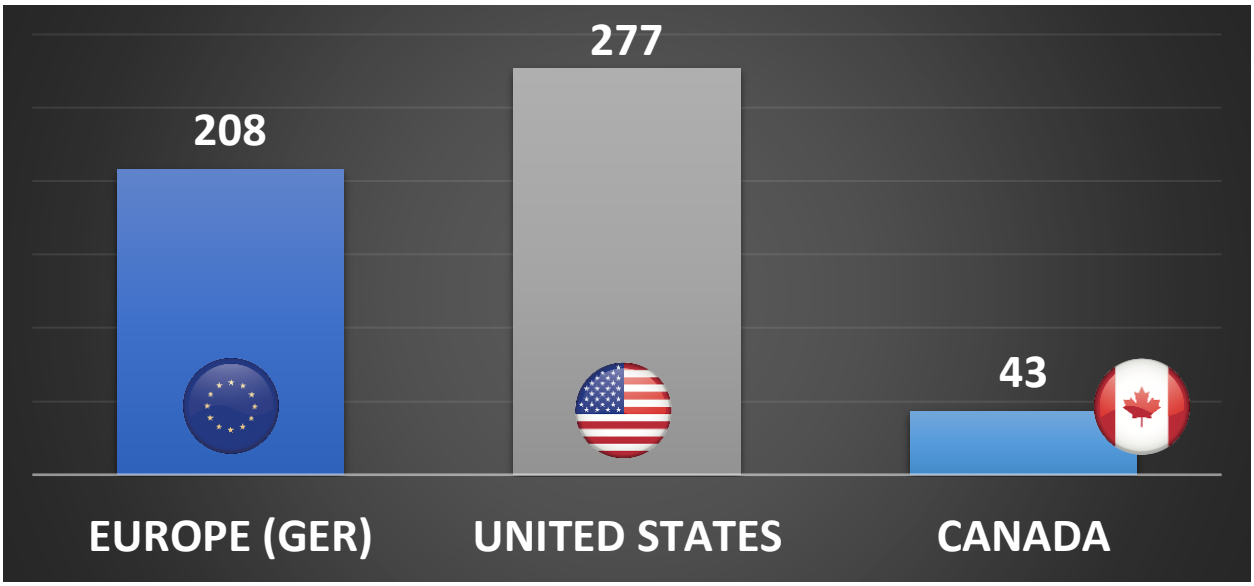
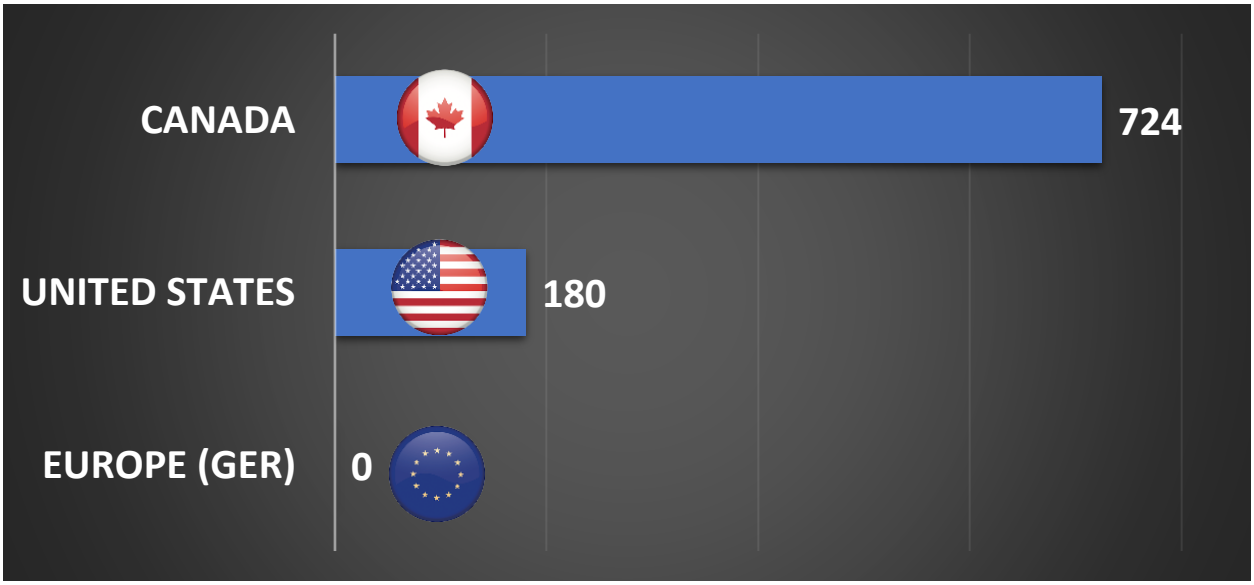


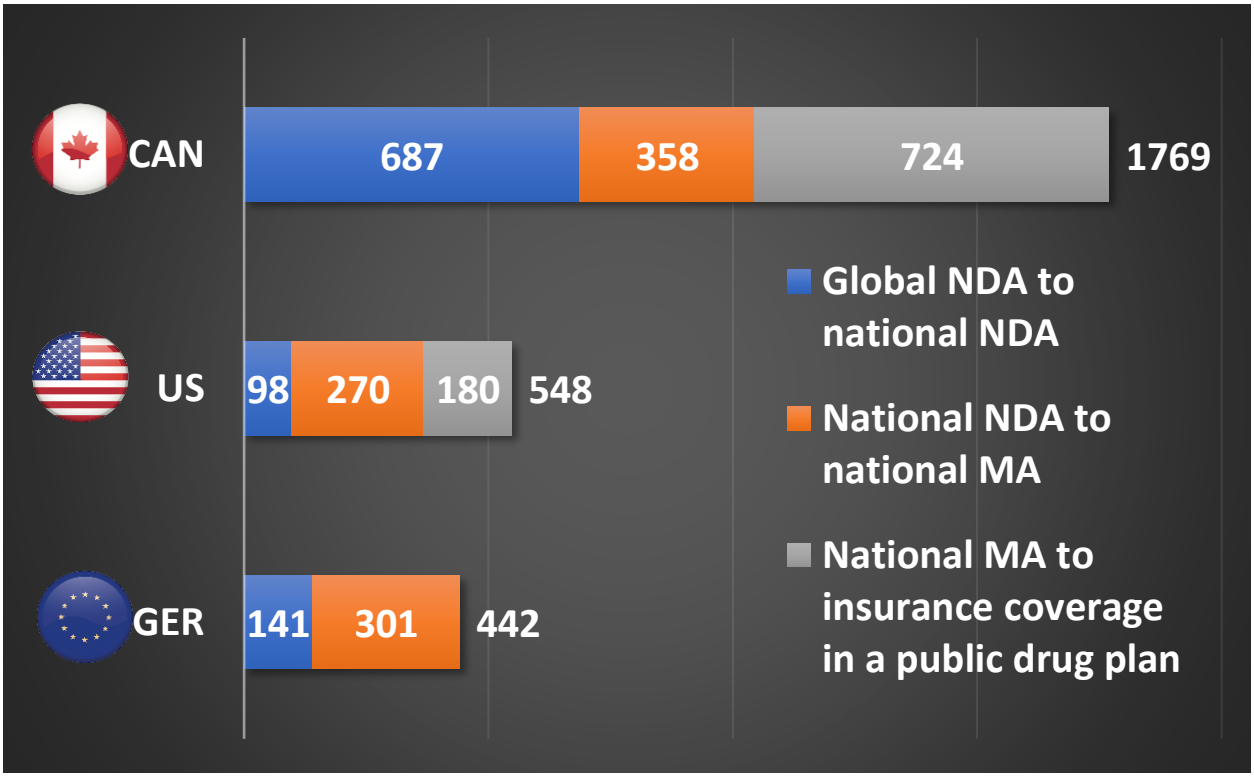
EXHIBIT 7. Average number of days between marketing authorization and formulary listing in public drug plans 2016-2021



TOTAL WAIT

EXHIBIT 8 shows the average number of days between first global launch and insured access in a public drug plan, for new active substances accruing marketing authorization during 2016–2020. The bars are presented in three segments showing the time from (1) global NDA to national NDA, (2) national NDA to national marketing authorization, and (3) national marketing authorization to public insurance coverage in Canada, US and Germany, as of the end of 2021. The total wait time to access new medicines in a public drug plan averaged 1,769 days in Canada, 368 to 548 days in the United States, and 442 days in Germany. On average publicly insured Canadians waited 1,221 to 1,401 days longer than Americans insured under Medicare to get access to a new medicine under their drug plan, and 1,327 days longer than publicly insured Germans to get access to a new medicine under their drug plan.

EXHIBIT 8. Total wait for new medicines in Canada, the EU and the US 2016-2021



POLICY DISCUSSION

Canada lags the EU, US

Canada ranks behind Europe and the United States on both the availability of, and the wait for access to new medicines. Canadians get access to only a fraction of the new drugs that are available to Europeans and Americans. Counting drug launches occurring during 2016-2020, Health Canada received 205 new drug applications, compared to 300 by the EMA and 333 by the FDA. Comparing the number of accrued marketing authorizations for new active substances issued by the three national regulators, Health Canada reported 182, while the EMA issued 208 and the FDA issued 277. Publicly insured Germans had access to 208 new medicines during the study period, publicly insured Americans had access to 277 new medicines, and publicly insured Canadians had access to only 43 new medicines.

Canadians also wait much longer than Europeans and Americans for new drug launches, for government to approve the new drugs that are launched in Canada, and for insurance coverage of new medicines. On average, Canadians waited 1.9 years after a new drug was launched in Europe or in the United States for the same new drug to be launched in Canada. A comparison of the domestic experience of the national regulators in each jurisdiction showed that the time between the date of a new drug application and the date of marketing authorization by Health Canada averaged more than 1 year, while the EMA averaged 0.82 years and the FDA averaged 0.74 years across all new active substances authorized for marketing in common with Health Canada. As previously mentioned, the effective formulary listing date for the United States and Germany is practically equivalent to the national marketing authorization date. Whereas the average delay from marketing authorization to formulary listing in Canada's public drug plans averaged almost 2 years. In total, on average publicly insured Canadians waited 3.2 to 3.8 years longer than Americans insured under Medicare to get access to a new medicine under their drug plan, and almost 3.6 years longer than publicly insured Germans to get access to a new medicine under their drug plan.

The country's lagging performance on these metrics can be explained by both structural and policy related factors. The size of the Canadian market is an obvious structural determinant of the country's low priority for new drug launches. Canada's market is characterized by a small population (not shown) with relatively high income **[EXHIBIT 9]** and ranks among the top 10 global pharmaceutical markets. **EXHIBIT 10** shows total national sales in US dollars for the top 10 global pharmaceutical markets stated as a percentage of total global pharmaceutical sales in 2020. Canada ranked ninth but was only 1.8% of the global market for pharmaceutical sales. By comparison, the United States accounted for almost 40%, and the top four European jurisdictions (Germany, France, Italy, and Spain) collectively accounted for 11.5% of the global market for pharmaceutical sales. **[11] [12]** Canada is not an insignificant market, but it is much less important than the United States and Europe. The structural disadvantage makes it imperative that federal and provincial governments address the policy determinants of new drug launches.

EXHIBIT 9. GDP per capita in US dollars for the top 10 global pharmaceutical markets and the EU 27 in 2020

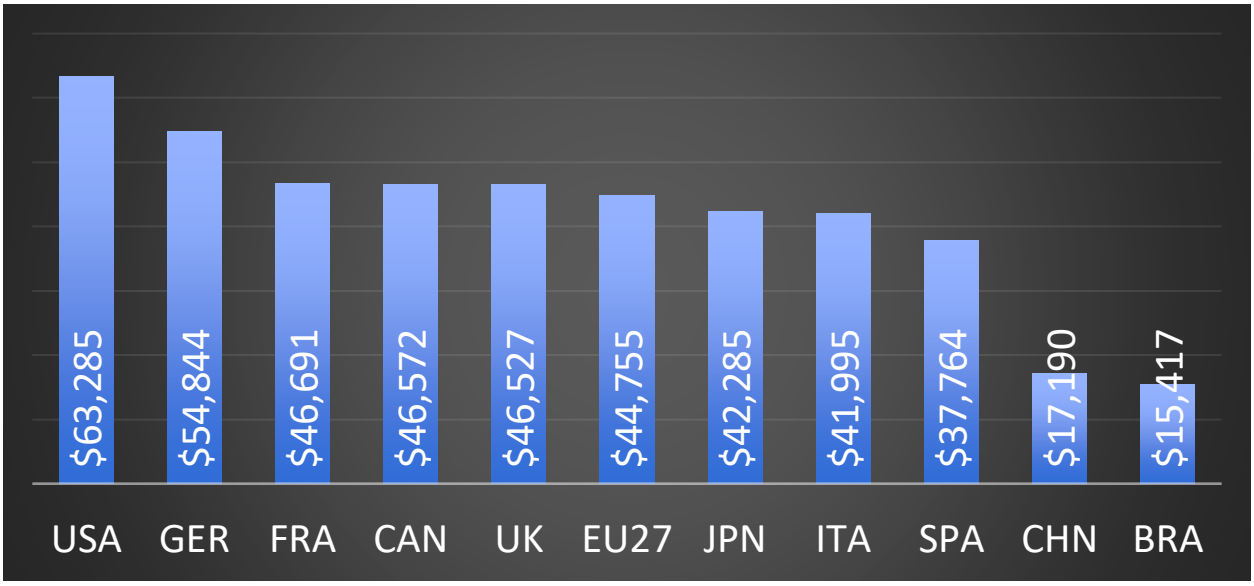
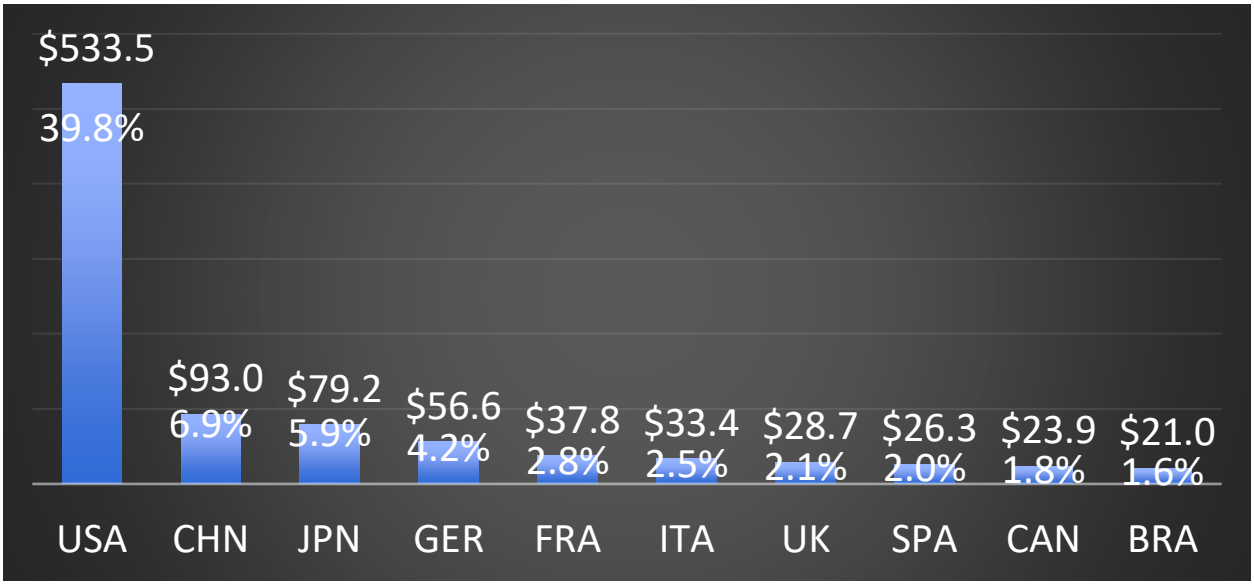


EXHIBIT 10. Total national sales in US dollars for the top 10 global pharmaceutical markets stated as a percentage of total global pharmaceutical sales in 2020



Price regulation

As a result of Canada's small market size, pharmaceutical pricing and reimbursement is an especially important policy determinant of its priority for new drug launches. Small markets can minimize their structural disadvantage by avoiding price controls. Research has shown that price regulation is a significant factor in company decisions about prioritizing markets for new drug launches. **[13] [14] [15] [16] [17] [18] [19]**

Recent policy changes are expected to cause a deterioration of the pharmaceutical pricing and reimbursement environment in Canada. In July 2022 the federal government intends to implement new price regulations that are intended to dramatically reduce the price ceiling permitted for new medicines launched in Canada. The government's estimate is that the regulations could reduce the maximum allowable prices for high-cost medicines by up to 52%. **[20]** The impact could be much larger. Case studies modeling the impact on several high-cost drug products found that the new regulations would have imposed price ceilings from 61% to 84% lower than the actual maximum allowed for those drugs. **[21] [22]** Recent court cases have struck down elements of the new regulations, making the actual impact on price difficult to predict. **[**23**]** However, the federal government still has opportunity to appeal. If all of the elements of the regulations were restored, the resulting price limits would disincentivize pharmaceutical firms from prioritizing the Canadian market when launching new medicines.

Instead, the federal government should end its price control regime, revoke the regulations and decommission the PMPRB. The Board's function is redundant. Several other agencies are involved in regulating the efficacy and price of new drugs. Moreover, total spending on patented medicines has accounted for a stable, small percentage of national health expenditures for 30 years. [**24]** Replacing price regulation with structured negotiation like the German model would increase incentives for companies to prioritize the Canadian market for new drug launches.

Expedited formulary listing

Germany provides a real-world model for expediting insurance coverage for new medicines that could be useful to inform discussion of this issue in Canada. The German system for pharmaceutical pricing and reimbursement in its public drug plans is based on structured negotiation instead of regulation and is designed to allow immediate interim insurance coverage following marketing authorization, with permanent insurance coverage pending the outcome of negotiations.

Under the German Medicines Market Reorganization Act (AMNOG) 2011, pharmaceutical manufacturers launching a new drug on the market, are free to set the price for a maximum of twelve months. Manufacturers must submit clinical evidence to the Federal Joint Committee (G-BA) that proves the additional benefit of the drug. If there is additional therapeutic benefit, the manufacturer negotiates the price at which the drug will be reimbursed by the statutory health insurance funds. Price negotiations must reach agreement within six months. If no agreement can be reached, an arbitration board decides on the reimbursed price using European reference prices. There is an appeal process. Drugs lacking evidence of additional therapeutic benefit are reimbursed in the reference group price system. **[25]**

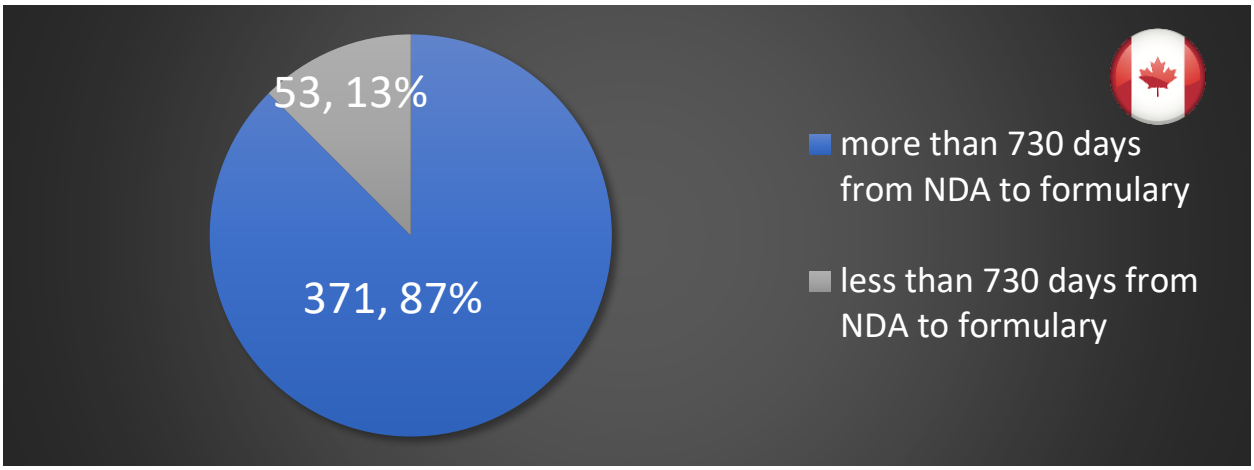
Applying this model to Canada, the federal price regulations would be eliminated. New active substances would be listed on drug plan formularies immediately following the first market authorization issued by the EMA/FDA/Health Canada. The initial formulary list price would be the manufacturer's suggested price and would be used as a benchmark for rebates negotiated with the pCPA or directly with the drug plans. Negotiations would be informed, but not determined, by publicly available international reference prices and the HTA process. When negotiations were complete, the difference between the manufacturer's suggested price and the negotiated price would be retrospectively applied to sales that occurred in the interim period. Negotiations would be time limited and if agreement could not be reached, would progress to arbitration. The formulary listing would expire if either party rejected the arbiter's price and revenues earned under the interim price would be rebated according to the arbiter's price. Manufacturers would have the option to request renegotiation in the future if new clinical or cost effectiveness data emerged, or any other circumstances changed the value proposition of the drug product. The pCPA would be obliged to accommodate a second round of negotiation.

The proposed changes would expedite insured access to new drugs while leaving the bargaining leverage of the payer (formulary exclusion) and the seller (withholding product) ultimately intact. Adopting this policy change could reduce wait time by up to 724 days for publicly insured Canadians, equal to the current average time spent from Health Canada marketing authorization to formulary listing in a public drug plan. [**EXHIBIT 7**]

Patent term restoration (PTR)

Intellectual property (IP) protection is another policy determinant of company decisions about prioritizing markets for new drug launches. **[26]** Canada currently has a patent term restoration regime that offers research-based pharmaceutical companies the potential to recover up to two years of time lost on their patent because of lengthy regulatory and government approval processes. Restoration is calculated from the filing date of the patent application to the date of marketing approval, up to a maximum of two years. PTR does not compensate for subsequent delays caused by HTA, pCPA negotiations and federal-provincial public formulary listing agreements. The data indicate the delay caused by reimbursement processes is as significant as the delay from regulatory processes. We counted the number of formulary listings of NAS that experienced total waits (HC NDA to formulary listing) exceeding the two-year (730 days) limit for PTR. Multiplying the 182 new active substances authorized for marketing by Health Canada from 2016–2020 across 11 federal and provincial public drug plans indicated that there were 2,002 total potential formulary listing opportunities from 2016 to 2021. The number of actual formulary listings across the 182 NAS and 11 public drug plans totaled 424 (21% of 2,002). **EXHIBIT 11** shows that 371 (87% of 424) of these experienced total waits exceeding the two-year limit for PTR. For these new drugs, the maximum wait recorded was 2,457 days (6.7 years) from NDA to formulary listing. The average wait recorded was 1,215 days (3.3 years). The erosion of time under market exclusivity is likely a major reason why pharmaceutical companies deprioritize the Canadian market for new drug launches. Extending patent term restoration to compensate for a full recovery of all time lost from the filing of a new drug application to formulary listing would remove IP related disincentives to launching new drugs earlier in Canada.

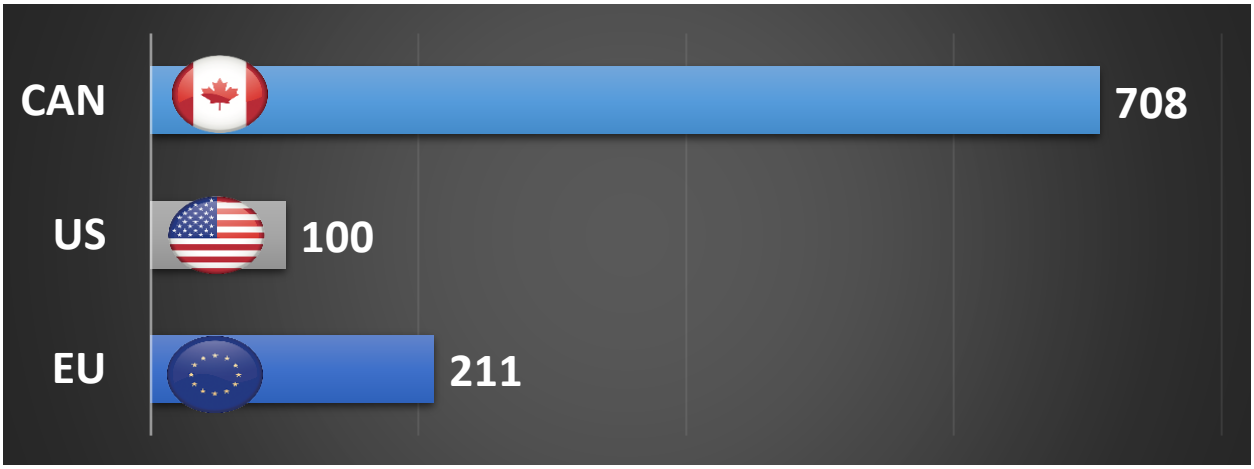
EXHIBIT 11. Number of formulary listings with total waits exceeding the 2-year limit for PTR



Regulatory harmonization

The availability and wait for new drugs could be improved through regulatory harmonization under which, Health Canada would automatically and immediately recognize new drug approvals occurring first in either the EMA or the FDA. Health Canada could implement this policy unilaterally without requiring mutual recognition. Scientific standards for new drug applications are the same for Health Canada, the EMA and the FDA. Regulatory harmonization could have potentially made an additional 168 new drugs available to Canadians, equal to the difference between the total number of unique marketing authorizations across all three jurisdictions (350) and the number of marking authorizations actually issued by health Canada (182). The policy also could have reduced the overall wait by the current average time spent from first global marketing authorization to marketing authorization by Health Canada, which was 708 days **[EXHIBIT 12]**, minus the launch priority delay. If the launch priority delay for Canada was as short as the US, regulatory harmonization could have potentially saved 610 days, and if it was as short as the EU, could have saved up to 567 days.

EXHIBIT 12. First global marketing authorization to national marketing authorization 2016-2020



APPENDIX

EXHIBIT A. 182 drugs authorized for marketing by Health Canada 2016-2020

Brand Name	Ingredient(s)
ADDYI	FLIBANSERIN
ADLYXINE	LIXISENATIDE
ADYNOVATE	ANTIHEMOPHILIC FACTOR (RECOMBINANT), PEGYLATED
AFSTYLA	LONOCTOCOG ALFA
AIMOVIG	ERENUMAB
AJOVY	FREMANEZUMAB
AKLIEF	TRIFAROTENE
AKYNZEO	PALONOSETRON HYDROCHLORIDE, NETUPITANT
ALECENSARO	ALECTINIB HYDROCHLORIDE
ALUNBRIG	BRIGATINIB
ANTHIM	OBILTOXAXIMAB
ANTHRASIL	ANTHRAX IMMUNE GLOBULIN (HUMAN)
BALVERSA	ERDAFITINIB
BAT	BOTULINUM ANTITOXIN SEROTYPE
BAVENCIO	AVELUMAB
BELSOMRA	SUVOREXANT
BEOVU	BROLUCIZUMAB
BEPREVE	BEPOTASTINE BESILATE
BESPONSA	INOTUZUMAB OZOGAMICIN
BIKTARVY	EMTRICITABINE, BICTEGRAVIR SODIUM, TENOFOVIR ALAFENAMIDE HEMIFUMARATE
BLEXTEN	BILASTINE
BRIDION	SUGAMMADEX
BRINAVESS	VERNAKALANT HYDROCHLORIDE
BRINEURA	CERLIPONASE ALFA
BRIVLERA	BRIVARACETAM
CABLIVI	CAPLACIZUMAB
CABOMETYX	CABOZANTINIB
CALQUENCE	ACALABRUTINIB
CERDELGA	ELIGLUSTAT TARTRATE
CINQAIR	RESLIZUMAB
CORZYNA	RANOLAZINE
COTELLIC	COBIMETINIB FUMARATE
CRESEMBA	ISAVUCONAZONIUM SULFATE
CRYSVITA	BUROSUMAB
DACOGEN	DECITABINE
DARZALEX	DARATUMUMAB
DATSCAN	IOFLUPANE (123I)
DAURISMO	GLASDEGIB
DAYVIGO	LEMBOREXANT
DEFITELIO	DEFIBROTIDE
DEMYLOCAN	DECITABINE
DUPIXENT	DUPILUMAB
EMGALITY	GALCANEZUMAB
EMPLICITI	ELOTUZUMAB
ENSPRYNG	SATRALIZUMAB
EPCLUSA	VELPATASVIR, SOFOSBUVIR
ERLEADA	APALUTAMIDE
ESPEROCT	ANTIHEMOPHILIC FACTOR VIII (RECOMBINANT, B-DOMAIN TRUNCATED), PEGYLATED
EUCRISA	CRISABOROLE
EVENITY	ROMOSOZUMAB
FASENRA	BENRALIZUMAB
FIRDAPSE	AMIFAMPRIDINE PHOSPHATE
FOLOTYN	PRALATREXATE
GALAFOLD	MIGALASTAT HYDROCHLORIDE
GALLI EO	GALLIUM (68GA) CHLORIDE
GALLIAPHARM	GERMANIUM (68GE) CHLORIDE, GALLIUM (68GA) CHLORIDE
GIVLAARI	GIVOSIRAN
HEMLIBRA	EMICIZUMAB

IBRANCE	PALBOCICLIB
IBSRELA	TENAPANOR
IDELVION	ALBUTREPENONACOG ALFA
IDHIFA	ENASIDENIB MESYLATE
IMFINZI	DURVALUMAB
INCRELEX	MECASERMIN
INQOVI	DECITABINE, CEDAZURIDINE
INREBIC	FEDRATINIB HYDROCHLORIDE
INTRAROSA	PRASTERONE
JIVI	ANTIHEMOPHILIC FACTOR (RECOMBINANT, B-DOMAIN DELETED, PEGYLATED)
KANUMA	SEBELIPASE ALFA
KEVZARA	SARILUMAB
KISQALI	RIBOCICLIB SUCCINATE
KYMRIAH	TISAGENLECLEUCEL
KYPROLIS	CARFILZOMIB
LANCORA	IVABRADINE HYDROCHLORIDE
LARTRUVO	OLARATUMAB
LIBTAYO	CEMIPLIMAB
LIXIANA	EDOXABAN
LOKELMA	SODIUM ZIRCONIUM CYCLOSILICATE
LONSURF	TIPIRACIL HYDROCHLORIDE, TRIFLURIDINE
LORBRENA	LORLATINIB
LUTATHERA	LUTETIUM (177LU) OXODOTREOTIDE
LUXTURNA	VORETIGENE NEPARVOVEC
LYNPARZA	OLAPARIB
MAR-TRIENTINE	TRIENTINE HYDROCHLORIDE
MAVIRET	PIBRENTASVIR, GLECAPREVIR
MAYZENT	SIPONIMOD
MDK-NITISINONE	NITISINONE
MICTORYL, MICTORYL PEDIATRIC	PROPIVERINE HYDROCHLORIDE
MONOFERRIC	IRON ISOMALTOSIDE 1000
MYLOTARG	GEMTUZUMAB OZOGAMICIN
NERLYNX	NERATINIB MALEATE
NETSPOT	OXODOTREOTIDE
NEURACEQ	FLORBETABEN (18F)
NINLARO	IXAZOMIB CITRATE
NITISINONE TABLETS	NITISINONE
NUBEQA	DAROLUTAMIDE
OCALIVA	OBETICHOLIC ACID
OCREVUS	OCRELIZUMAB
ODOMZO	SONIDEGIB
OLUMIANT	BARICITINIB
ONPATTRO	PATISIRAN SODIUM
ONSTRYV	SAFINAMIDE
ORFADIN	NITISINONE
ORILISSA	ELAGOLIX
ORKAMBI	LUMACAFTOR, IVACAFTOR
OXERVATE	CENEGERMIN
OZANEX	OZENOXACIN
OZEMPIC	SEMAGLUTIDE
PANHEMATIN	HEMIN
PIFELTRO	DORAVIRINE
PIQRAY	ALPELISIB
POLIVY	POLATUZUMAB VEDOTIN
PORTRAZZA	NECITUMUMAB
PRALUENT (PFP), PRALUENT (PFS)	ALIROCUMAB
PRAXBIND	IDARUCIZUMAB
PREVYMIS	LETERMOVIR
PROCYSBI	CYSTEAMINE BITARTRATE
QINLOCK	RIPRETINIB
RADICAVA	EDARAVONE
RAPIVAB	PERAMIVIR
RAVICTI	GLYCEROL PHENYLBUTYRATE
RAYALDEE	CALCIFEDIOL

REBINYN	COAGULATION FACTOR IX (RECOMBINANT), PEGYLATED
REBLOZYL	LUSPATERCEPT
REKOVELLE	FOLLITROPIN DELTA
REXULTI	BREXPIPRAZOLE
RINVOQ	UPADACITINIB
ROZLYTREK	ENTRECTINIB
RUPATADINE	RUPATADINE FUMARATE
RUZURGI	AMIFAMPRIDINE
RYDAPT	MIDOSTAURIN
SARCLISA	ISATUXIMAB
SILIQ	BRODALUMAB
SKYRIZI	RISANKIZUMAB
SPINRAZA	NUSINERSEN SODIUM
STEGLATRO	ERTUGLIFLOZIN
SUNVEPRA	ASUNAPREVIR
SYMDEKO	TEZACAFTOR, IVACAFTOR
TAGRISSO	OSIMERTINIB, OSIMERTINIB MESYLATE
TAKHZYRO	LANADELUMAB
TALTZ	IXEKIZUMAB
TALZENNA	TALAZOPARIB
TAVALISSE	FOSTAMATINIB DISODIUM
TECENTRIQ	ATEZOLIZUMAB
TEGSEDI	INOTERSEN SODIUM
TIBELLA	TIBOLONE
TOMVI	ETOMIDATE
TREMFYA	GUSELKUMAB
TRESIBA (FLEXTOUCH), TRESIBA (PENFILL)	INSULIN DEGLUDEC
TRULANCE	PLECANATIDE
TUKYSA	TUCATINIB
ULTOMIRIS	RAVULIZUMAB
UNITUXIN	DINUTUXIMAB
UPTRAVI	SELEXIPAG
VASCEPA	ICOSAPENT ETHYL
VEKLURY	REMDESIVIR
VELPHORO	SUCROFERRIC OXYHYDROXIDE
VELTASSA	PATIROMER SORBITEX CALCIUM
VENCLEXTA	VENETOCLAX
VERZENIO	ABEMACICLIB
VIBERZI	ELUXADOLINE
VITRAKVI	LAROTRECTINIB
VIZIMPRO	DACOMITINIB
VOCABRIA, CABENUVA	RILPIVIRINE, CABOTEGRAVIR
VONVENDI	VON WILLEBRAND FACTOR (RECOMBINANT), VONICOG ALFA
VOSEVI	VOXILAPREVIR, VELPATASVIR, SOFOSBUVIR
VYNDAQEL	TAFAMIDIS MEGLUMINE
VYZULTA	LATANOPROSTENE BUNOD
XENLETA	LEFAMULIN ACETATE
XERMELO	TELOTRISTAT ETIPRATE
XIIDRA	LIFITEGRAST
XOFLUZA	BALOXAVIR MARBOXIL
XOSPATA	GILTERITINIB FUMARATE
XTORO	FINAFLOXACIN
XYDALBA	DALBAVANCIN
YESCARTA	AXICABTAGENE CILOLEUCEL
ZEJULA	NIRAPARIB
ZEPATIER	GRAZOPREVIR, ELBASVIR
ZEPOSIA	OZANIMOD HYDROCHLORIDE
ZINBRYTA	DACLIZUMAB BETA
ZOLGENSMA	ONASEMNOGENE ABEPARVOVEC
ZONTIVITY	VORAPAXAR SULFATE

REFERENCES

[1] DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: new estimates of R&D costs. J Health Econ. 2016; 47:20-33. doi:10.1016/j.jhealeco.2016.01.012

[2] Canadian Health Policy Institute (CHPI). Evidence that innovative medicines improve health and economic outcomes: focused literature review. Canadian Health Policy, April 2019. www.canadianhealthpolicy.com

[3] Life Sciences Ontario. New Medicine Launches: Canada in a Global Context June 22, 2020.

[4] Health Canada. Biologics and Radiopharmaceutical Drugs Directorate Drug Submission Performance Annual Report, Fiscal Year 2020-2021, April 1 2020 - March 31 2021; Therapeutic Products Directorate Drug Submission Performance Annual Report, Fiscal Year 2020-2021, April 1 2020 - March 31 2021; Notice Of Compliance Database Extracts; Drug Products Database.

[5] IQVIA Inc. Integrated Market Access Console (IMAM) Database. 21 December 2021.

[6] Statistics Canada. Table 17-10-0005-01 Population estimates on July 1st, by age and sex.

[7] Government of Canada (2021). Non-Insured Health Benefits program: First Nations and Inuit Health Branch: Annual report 2020 to 2021. Indigenous Services Canada.

[8] US Food and Drug Administration (FDA). PERFORMANCE REPORT TO CONGRESS for the Prescription Drug User Fee Act, 2016-2020; Compilation of CDER New Molecular Entity (NME) Drug and New Biologic Approvals.

[9] European Medicines Agency (EMA). European Public Assessment Reports (EPARs); EMA annual reports 2016-2020; monthly statistics reports 2016-2020.

[10] U.S. Centers for Medicare & Medicaid Services. (2022). Medicare Prescription Drug Benefit Manual Chapter 6 – Part D Drugs and Formulary Requirements.

[11] IQVIA Inc. MIDAS database December 2020.

[12] IQVIA Market Prognosis. September 2021, IQVIA institute. The Global Use of Medicines 2022.

[13] Skinner, Brett (2021). Rogue Regulator: PMPRB's false narrative is driving dangerous drug price controls. Chapter 3. Canadian Health Policy Institute. ISSN 2562-9492 https://doi.org/10.54194/YQYB2454 www.canadianhealthpolicy.com

[14] Patricia M. Danzon, Y. Richard Wang and Liang Wang (2005). The impact of price regulation on the launch delay of new drugs – evidence from twenty-five major markets in the 1990s. Health Economics, 14: 269–292 (2005).

[15] Margaret K. Kyle (2007). Pharmaceutical Price Controls and Entry Strategies. Review of Economics and Statistics, Volume 89 | Issue 1 | February 2007 p.88-99.

[16] Patricia M. Danzon and Michael F. Furukawa (2008). International Prices and Availability of Pharmaceuticals In 2005. Health Affairs 27, no. 1 (2008): 221–233; 10.1377/hlthaff.27.1.221.

[17] Joan Costa-i-Font, Nebibe Varol, Alistair McGuire (2011). Does price regulation affect the adoption of new pharmaceuticals? The Centre for Economic Policy Research.

[18] Nebibe Varol & Joan Costa-i-Font & Alistair McGuire (2011). Explaining Early Adoption of New Medicines: Regulation, Innovation and Scale. CESifo Working Paper Series 3459, CESifo Group Munich.

[19] Panos Kanavos, Anna-Maria Fontrier, Jennifer Gill, Olina Efthymiadou (2019). Does external reference pricing deliver what it promises? Evidence on its impact at national level. The Journal of Health Economics.

[20] Regulations Amending the Patented Medicines Regulations (2019).

[21] Rawson, Nigel SB; Lawrence, Donna (2020). New Patented Medicine Regulations in Canada: Updated Case Study of a Manufacturer's Decision-Making about a Regulatory Submission for a Rare Disorder Treatment. Canadian Health Policy, January 2020. www.canadianhealthpolicy.com

[22] PDCI (2020). Impact Analysis of The Draft PMPRB Excessive Price Guidelines.

[23] Jospé, Dara and Mathieu Gagné (2022). The PMPRB: Where Are We Now and What's Next? Canadian Health Policy, MAR 2022. ISSN 2562-9492, https://doi.org/10.54194/DBAD7639, www.canadianhealthpolicy.com

[24] Canadian Health Policy Institute (CHPI) (2021). Patented Medicines Expenditure in Canada 1990-2019. Canadian Health Policy, June 2021. ISSN 2562-9492 www.canadianhealthpolicy.com.

[25] OECD (2018). Pharmaceutical Reimbursement and Pricing in Germany. Organisation for Economic Cooperation and Development.

[26] Cockburn, Iain M., Jean O. Lanjouw, and Mark Schankerman (2016). "Patents and the Global Diffusion of New Drugs." American Economic Review, 106 (1): 136-64.