

An Empirical Examination of the Patented Medicine Prices Review Board Price Control Amendments on Drug Launches in Canada

Oliver Spicer^{1,2} and Paul Grootendorst^{1,3}

1. Leslie Dan Faculty of Pharmacy, University of Toronto
2. Astellas Pharma Canada, Inc.
3. WHO Collaborating Centre for Governance, Transparency and Accountability in the Pharmaceutical Sector, University of Toronto

July 28, 2020

Author Contributions: Both authors contributed equally to the paper and approved the final version of the article.

Declaration of Conflicting Interests: Paul Grootendorst has provided expert testimony and or reports in legal proceedings on behalf of both innovator and generic drug companies.

Funding: The authors received no financial support for the research, authorship and/or publication of this article. Innovative Medicines Canada (IMC) provided data used in a report that was published in January 2019.

Oliver Spicer is a PhD student at the University of Toronto and paid employee of Astellas Pharma Canada, Inc. (Astellas). This article is intended for informational purposes only and does not replace independent professional judgment. Positions taken and opinions expressed are those of the author individually and, unless expressly stated to the contrary, do not necessarily reflect the opinion or position of the author's employer, Astellas, or any of its subsidiaries and/or related entities. Other than the author's direct contribution, Astellas had no role in the study design, interpretation of results, or decision to publish.

Abstract

The Government of Canada plans to implement new controls on prices of patented drugs in January 2021. The literature indicates that such controls delay drug launches. The Government's unpublished analysis suggests that no delays will occur. To examine this claim, we use recent OECD country level data to estimate regression models of launch delays. These models suggest that the new price controls will indeed delay access to new medicines in Canada.

Introduction

Canada's Patented Medicine Prices Review Board (PMPRB) regulates the introductory prices of patented drugs and their rate of increase over time.¹ The price regulatory agency, established in 1987, has been criticized because the list prices for patented drugs in Canada are high by international standards.² There are structural reasons for this: drugs that the PMPRB deems to be therapeutically novel can be priced no higher than the median of the list prices of the same drug in seven countries – the so-called PMPRB7. These seven countries are the United Kingdom, France, Italy, Sweden, Germany, Switzerland, and the United States. Historically, the latter three countries have had amongst the highest drug prices globally.³⁻⁸ Thus, if the price ceiling is binding, domestic list prices of therapeutically novel drugs in Canada will be about the fourth highest globally. Prices of new drugs that are therapeutically similar to established drugs, colloquially known as “me-too” drugs, can be priced no higher than the established drugs. But the established drugs will typically include those deemed earlier to be therapeutically important – whose list prices are set using the international pricing test – so that the list prices of follow-on drugs will also be high.

In practice, few customers pay these list prices. Multinational drug companies price discriminate by giving drug plans confidential rebates off of public list prices.^{3,9} It is therefore difficult to assess how actual net-of-rebate prices paid in Canada compare to those paid elsewhere. Nevertheless, there is some evidence that prices actually paid in Canada are higher than those paid in other high-income countries such as the UK, France and Australia.^{10,11}

For the past several years, the PMPRB has considered approaches to lower both list and actual prices.¹²⁻¹⁴ It has recently unveiled the new pricing rules.¹⁵ First, the PMPRB will change the set of comparator countries, replacing the two countries with the highest drug list prices in the PMPRB7 – the US and Switzerland – with six countries that tend to have lower list prices than Canada: Japan, Australia, Norway, Spain, Belgium and the Netherlands. When the new regulations come into force – in January 2021 – the interim maximum list price of a new patented drug sold in Canada will be limited to the median of the list prices of the same drug in these 11 countries, or more precisely, the median list price in the subset of these countries in which the drug has already launched.¹⁵ This interim period will last for a maximum of three years or until a pharmaceutical company provides international prices for at least five of the PMPRB11 countries, after which the maximum list price is established. In situations where no reference prices are available, the maximum list price will be set based on the prices of therapeutically similar drugs.¹⁵

A second change introduced in the new PMPRB pricing rules are caps on actual (i.e., post-rebate) prices paid in Canada. Price ceilings for high cost drugs – those with annualized treatment costs greater than 150% of Canada's per-capita gross domestic product (GDP) – will depend on the drug's estimated cost-effectiveness.¹⁵ Drugs which are anticipated to have high sales volumes – in excess of \$50 million – will be subject to additional price caps.¹⁵

Cost effectiveness assessments require estimates of how much more effective a new drug is relative to the Canadian standard of care therapy, and the resource costs of both the new drug and standard of care. The PMPRB intends to measure the health gains using the “quality adjusted life year” or QALY, a measure that combines the length of life and the health-related quality of life. The resource costs of the new drug reflect the cost of the treatment itself plus any ancillary costs, such as the cost of administering it, as well as healthcare costs offset by the drug’s use. These estimates will be produced by the Canadian Agency for Drugs and Technologies in Health (CADTH) and its sister organization in Quebec, the Institut national d’excellence en santé et en services sociaux (INESSS). The estimated values will be used to construct a new drug’s incremental cost effectiveness ratio or “ICER” – the ratio of additional resource costs over health gains.

Limits on transaction prices, expressed as a statutory percentage reduction off of the maximum list prices, will be greatest for high-cost drugs with the least therapeutic benefit and with the largest anticipated market size. For high-cost drugs, the PMPRB will leverage the CADTH/INESSS ICER estimates for drugs with an annual expected market size of \$12-\$50 million. For example, a high-cost breakthrough drug will have a willingness to pay threshold of \$200K/QALY and a price reduction floor of 20%.¹⁵ Conversely, a high-cost “me too” drug will have a \$150K/QALY threshold and a price reduction floor of 50%.¹⁵ Above \$50 million in market size, a drug is also considered a high sales volume drug and will be subject to additional price reductions. For drugs with sales between \$50-\$100 million, an additional 25% price reduction will be applied to transactions. When sales exceed \$100 million, this is increased to 35%. If a patentee’s annual revenues subsequently fall due to less units sold, the price reductions will not be readjusted.¹⁵

The new price controls proposed by the PMPRB, to the extent that they lower prices, will benefit payers, particularly private drug plans. However, the policy also generates costs. Some of these costs were estimated in the federal government’s cost benefit analysis (CBA) of the proposed policy change. One such cost is the proposed doubling of the PMPRB operating budget, as a larger staff complement is needed to administer the new pricing tests.¹⁶ Another potential cost of the price controls – ignored in the CBA – is the cost to consumers and drug payers associated with delayed launches of new drugs into Canada.¹⁷⁻¹⁹

On its face, it is unclear why a drug company would delay a drug launch in Canada on account of a price cut. One *could* imagine situations in which a price cut would render a Canadian launch unprofitable. This would occur if the sales revenues do not cover variable production costs as well as market entry and selling costs (such as the cost of obtaining regulatory approval, negotiating with drug plans, and marketing). It is less clear why a price cut would delay a market launch, if anticipated net revenues remain positive.

The academic literature has identified two reasons why delays may occur. First, drug companies typically do not have the personnel needed to obtain market authorization

from all target countries at once. Thus, they will prioritize launching in countries where gross profits are expected to be greatest.¹⁹ Canada's use of more stringent price controls, to the extent that they reduce actual prices, will reduce gross profits and thus lower Canada's launch priority.

Second, some countries use the PMPRB's model of international price referencing, wherein the maximum domestic drug price depends on foreign list prices. To illustrate, suppose that drug price regulators in country A set maximum prices in part on the basis of list prices in a smaller market, country B. If country B lowers its list prices, a multinational drug company may delay launches in B so that regulators in A cannot refer to B's prices when establishing price ceilings. This sacrifices some profits in B to preserve even greater profits in A.

By changing the set of comparator countries, the PMPRB will reduce Canada's public drug list prices. Will this cause drug companies to delay or reduce launches in Canada? Currently, Canadian drug prices are used to set maximum prices in at least five other countries, none of which have large pharmaceutical markets: Egypt, Brazil, Colombia, South Africa and Taiwan.²⁰⁻²³ It is unlikely a company would delay a launch in Canada to attain a higher list price in these countries. However, there is a risk that relatively large countries will begin to reference Canadian drug prices should Canada markedly lower its prices. For instance, the United States, whose pharmaceutical market is 22 times larger than Canada's, has recently proposed referencing Canadian prices to set prices for its Medicare Part B drug plan.^{4,24,25} The US Democratic party has made similar proposals.²⁶ Thus there is some risk that once the PMPRB regulations are enacted, drug companies will delay launches in Canada to prevent price declines in larger markets.

The Government of Canada claims that its new price tests will not delay drug launches because, based on its (unpublished) analysis of the international evidence, "list prices do not appear to be an important determinant of medicine launch sequencing".²⁷ This finding is at odds with the literature on drug launch timing.¹⁷⁻¹⁹ However, this literature may now be out of date as it relies on older data, mostly from the 1990s. The most recent data point used in the extant studies is from 2003. Since then actual prices have diverged from list prices owing to the increased use of confidential rebates.⁹

The goal of this paper is to examine recent data on drug launches and patented drug list prices for various OECD countries to inform the impact of the PMPRB regulatory changes on drug launch delays in Canada. We use these data to estimate regression models of country-level drug launches. Launches in a country are posited to depend on domestic list prices and market size, both of which were key explanatory variables in the earlier studies.^{18,28,29} We find that patented drug list prices still exert an economically important effect on launch decisions, holding other factors constant. We use this model to predict the impact of the forthcoming PMPRB regulatory changes on drug launches in Canada.

Methods

Like the earlier studies, we model how patented drug prices and market size affects the availability of new drugs in a country. However, our approach differs from the extant literature in several ways. The earlier studies estimated models of drug-specific launch lags, namely the time between first global launch of drug j and the drug's launch in country i . To account for censored durations – drugs that had not yet launched in country i at the time that the durations were measured – the studies have estimated durations models using maximum likelihood. The models include covariates that reflect the profitability of launching drug j in country i . The most definitive study, that by Danzon and Epstein (2012), focussed on launch timing in fifteen countries of drugs that were introduced globally over the period 1992-2003. The model includes the average list price of established drugs that are in the same therapeutic class as drug j in country i , controls for the number of branded and generic drugs in this class, the total unit sales volume of all these drugs, and an indicator of whether drug j was produced by a company with headquarters in country i . The models include country, year, and therapeutic class fixed effects; the total number of parameters estimated appears to be well in excess of 40.

Our models are much simpler. Instead of modeling drug-specific launch delays, we estimate linear regression models of the fraction of drugs launched globally over various periods of time that are available in OECD country i by a given date. We use data on all but 6 OECD countries: Colombia, Denmark, Iceland, Israel, Latvia and Lithuania. In our models, $Launch\%_i$ – the percentage of globally launched drugs launched in country i – is posited to depend on $price_i$, a patented drug price index for country i ; two measures of market size: pop_i , the population of country i , and GDP/pop_i , the (expenditure-based) per capita gross domestic product of country i ; and, finally, ema_i , an indicator of whether country i is a member of the European Medicines Agency (EMA). (EMA-approved drugs are approved for sale in all EMA member countries.) Whereas the Danzon and Epstein model was estimated using the complementary log–log duration model with normally distributed drug-level heterogeneity, we estimate our model using ordinary least squares. Unlike standard duration models, our model naturally accommodates drugs that are never launched in a country.

$$Launch\%_i = \beta_0 + \beta_1 \log(price_i) + \beta_2 \log(pop_i) + \beta_3 \log(GDP/pop_i) + \beta_4 ema_i + \varepsilon_i$$

Measurement of launch percentage

The outcome variable, $Launch\%$, is measured as a ratio. The denominator is the number of drugs approved for use in any one of a group of countries over some period of time. The numerator is the number of these drugs that accrued a sale in country i by a certain date.

Launch% was measured using different time periods and country groups to assess the robustness of the results (Table 1). In model 1, the denominator in the launch variable is the number of new drugs approved during 2015 by the U.S. Food and Drug Administration (FDA), the EMA, or Health Canada. The model 1 numerator is the number of these drugs that accrued a sale in OECD country i between the first quarter of 2015 and the third quarter of 2016. The outcome variables in models 2 and 3 differ only in the time intervals for the numerator and denominator, as outlined in Table 1. The outcome variable in models 4 and 5 differ in two respects. First, the denominator is the number of new drugs approved by a slightly different set of regulatory bodies. Second, both the numerator and denominator account for sale accruals and drug approvals, respectively, over longer time intervals than in models 1, 2, and 3. These models therefore provide estimates of the impact of drug price (and other covariates) on drug launches over a longer-term period. One would expect that price would have a smaller impact on drug launches over the longer term.

Table 1: Summary of Model Inputs

		Single Year Models			Multi-Year Models	
		Model 1	Model 2	Model 3	Model 4	Model 5
Launch% _{<i>i</i>}	Numerator*	2015-2016Q3	2016-2017Q3	2017-2018Q3	2009-2018Q3	2011-01/2018-08
	Denominator¥	2015	2016	2017	2009-2017	2011-01/2018-08
	Regulatory Bodies	FDA, EMA or HC	FDA, EMA or HC	FDA, EMA or HC	FDA, EMA, HC or Swiss	FDA, EMA or Japan
Price _{<i>i</i>}		2015	2016	2017	Average of 2014, 2015, 2016, 2017	2017
Population _{<i>i</i>}						
GDP _{<i>i</i>} /pop _{<i>i</i>}						
ema _{<i>i</i>}		Indicator variable for membership within the EMA				

*Period during which approved drugs accrued a sale in country.

¥ Period during which a drug was approved by any of the regulatory bodies. FDA is the United States Food and Drug Administration; EMA is the European Medicines Agency; HC is Health Canada. Swiss refers to Swissmedic, the medicines regulatory authority for Switzerland. Japan refers to the Japanese Pharmaceuticals and Medical Devices Agency.

Data for *Launch%* in models 1 and 2 were respectively obtained from the 2016 and 2017 “Meds Entry Watch” reports produced by the National Prescription Drug Utilization Information System (NPDUIS) – a publicly funded research initiative.^{30,31} Data for models 3 and 4 were obtained from the 2018 edition of the same report.³² Data for model 5 were obtained from a 2019 report published by Innovative Medicines Canada (IMC) – a group representing Canada’s innovative pharmaceutical industry.³³ Both the NPDUIS and IMC reports used country-level sales data collected by IQVIA, a pharmaceutical market research firm formerly known as IMS Health.

Measurement of covariates

In all models, *Launch%* was posited to depend on an index of patented drug prices, market size, and market entry costs. The patented drug price index, $price_i$, used in models 1-4, were obtained from the 2014-2017 PMPRB Annual Reports. The price index is a weighted average of the ratios of the country i to Canadian price for each patented drug sold in both countries during a particular year. The weights in this weighted average reflect Canadian sales during the year. The PMPRB obtained the price data from IQVIA's MIDAS database.⁵⁻⁸ The MIDAS data are derived from the purchase invoices of a sample of pharmacies in each country. Invoiced prices reflect wholesaler markups; IQVIA removes estimates of these markups in order to determine the prices paid to drug manufacturers. Foreign prices are converted into Canadian dollars using 36-month average exchange rates. The prices do not reflect off invoice rebates paid by drug manufacturers to drug payers. For model 5, pricing data was obtained from IMC, which reports the weighted average price of global drugs during 2017.³³ For this reason, other covariates included in model 5 were also from 2017.

The two measures of market size, expenditure-based GDP per capita and population size: GDP/pop_i , and pop_i , were measured using the Penn World Tables database.³⁴ Market entry costs for country i were measured using ema_i , an indicator equal to one if country i is a member of the EMA. EMA-approved drugs are approved for sale in all EMA member countries. Thus, the cost of obtaining EMA regulatory approval is amortized over unit sales in the entire EMA region.³⁵ However, companies still face the cost of obtaining reimbursement in each of the countries.

One defect of models 4 and 5, which capture drug launches in a country over an 8-year period, is that the covariates reflect conditions in just one year. Degrees of freedom and data constraints preclude the inclusion in the model of covariates that reflect prices in each year of the accrual period. For instance, the PMPRB only began reporting price index data for all OECD countries in 2014 (prior to this, they only reported the PMPRB7 price indexes). Given these constraints, for Model 4 we use the average of the 2014-2017 data for all covariates. As a robustness check, we estimated a model using the same outcome variable but measuring the covariates at each of the years in numerator accrual period for which data is available. These results are reported in the Appendix.

We also estimate variants of the models that account for the influence of potential outliers in our data set. Specifically, the United States and New Zealand are known to be outliers with respect to drug launches and drug prices; the US has particularly large values of both variables (Figure 1). In contrast, New Zealand is often cited as having particularly low numbers of drug launches, though its prices as reported by the PMPRB are quite similar to Canada.^{4-8,33,36} To ensure that these two countries alone were not driving the results, we estimated variants of our models excluding their observations and report these in the Appendix.

Finally, we use our estimates to calculate the change in $Launch \%_i$ in response to 25%, 35%, and 45% reductions in $price_i$. We report the model standard error with these

calculations. We conduct Breusch Pagan tests for homoskedastic errors. The results of these tests are also reported in the Appendix.

Results

Figure 1 plots country level launch percentage against its price. This graph reveals a cluster of EMA member countries with higher launch percentages but lower patented drug prices than in Canada. This is consistent with the PMPRB’s claim that patented drug prices don’t affect drug launches. Launch percentages and prices in Switzerland – which is not a member of the EMA – are similar to those in Canada. South Korea and Turkey have relatively low prices and also relatively low launch fractions. Conversely, the United States have the highest drug prices and the highest launch fractions.

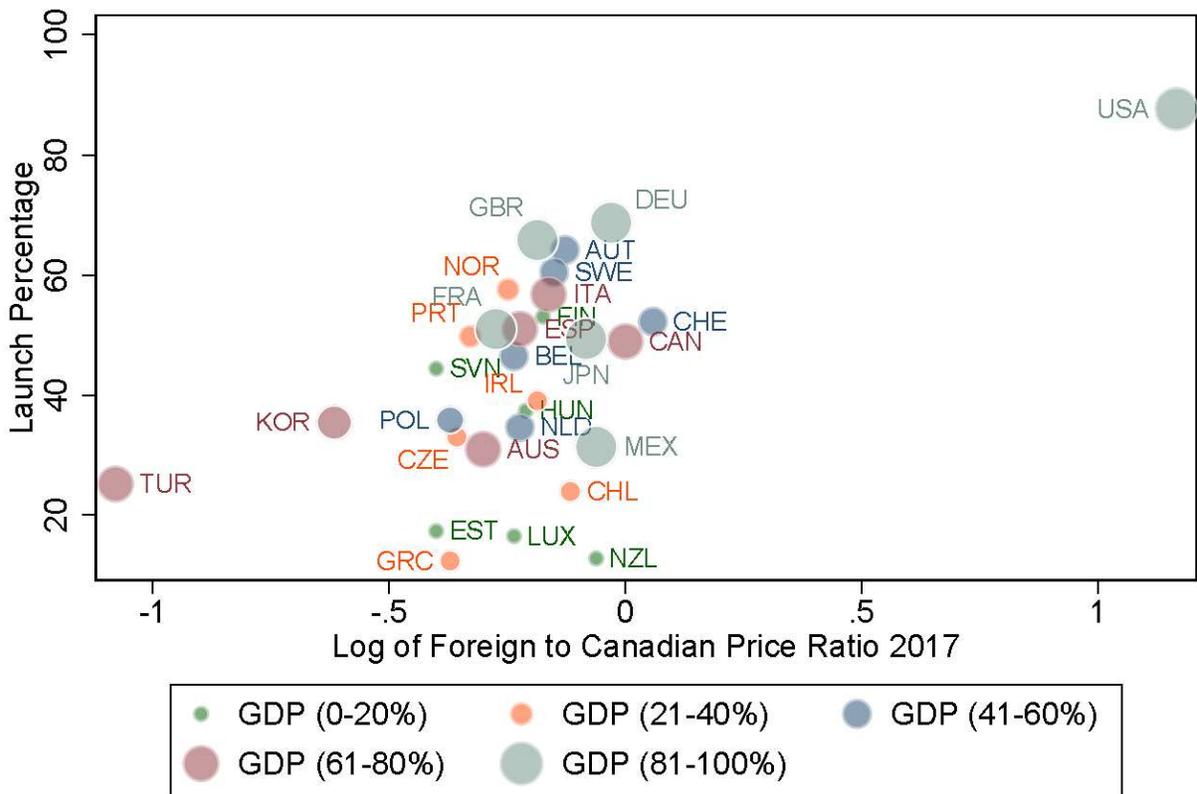


Figure 1. Launch percentage and log foreign to Canadian price, by country, 2017. Marker size proportional to total GDP. Model 3 launch percentage definition used.

We next turn to the estimates of the linear regression models to quantify the roles of drug price, market size and EMA membership on drug launch percentage. The tests of homoskedasticity, reported in the Appendix, could not be rejected at conventional significance levels.

1 Year Models

Models 1-3 capture the influence of covariates on drug launches over a period of 1-2 years. Relative price has an economically meaningful and statistically significant impact on launch fractions (Table 2). Higher values of GDP per capita, and population as well as EMA membership are also associated with larger launch fractions. The three models have adjusted R² values between 0.65-0.67. The OECD countries included in each model are those with sales data reported in the 2016-2018 Meds Entry Watch reports. In Model 1, Greece and Turkey are excluded because data for these countries was not reported in the 2016 report.

Table 2. Parameter estimates of 1-2 year models

Variable	Model 1 β (p-value)	Model 2 β (p-value)	Model 3 β (p-value)
log(price _i)	37.071** (0.001)	21.805** (0.002)	26.940*** (0.001)
log(population _i)	6.694** (0.001)	5.871*** (0.000)	6.343*** (0.001)
log(GDP _i /capita _i)	20.191** (0.007)	12.155* (0.029)	19.631** (0.005)
ema _i	15.246** (0.007)	15.311*** (0.000)	9.243 (0.054)
Constant	-207.118* (0.011)	-129.998* (0.033)	-206.145** (0.007)
N	29†	31	31
R ² adjusted	0.668	0.652	0.662

* p<0.05, ** p<0.01, *** p<0.001

†Launch Data for Greece and Turkey not available

7-8 Year Models

Models 4 and 5 capture the influence of price and market size on drug launch over a period of 7-8 years (Table 3). In these models, price has a smaller, although significant, impact on launch percentage. Per capita GDP is not significant in model 5. In Model 5, Slovakia was excluded because data were not reported.

Table 3. Parameter estimates of 7-8 year models

Variable	Model 4 β (p-value)	Model 5 β (p-value)
$\log(\text{price}_i)$	15.636* (0.027)	21.527*** (0.000)
$\log(\text{population}_i)$	7.048*** (0.000)	5.963*** (0.001)
$\log(\text{GDP}_i/\text{capita}_i)$	15.579* (0.011)	5.446 (0.425)
ema_i	13.855** (0.002)	9.822* (0.027)
Constant	-148.612* (0.025)	-12.620 (0.872)
N	31	30 [†]
R2 adjusted	0.668	0.609

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

[†]Launch Data for Slovakia was not available

The models were re-estimated after excluding observations for New Zealand and the United States. The results, reported in the Appendix, were generally unaffected by their exclusion.

Estimated impact of price reductions

We next used the parameter estimates to estimate the impact on expected drug launch percentage (and their standard errors) of a 25%, 35%, and 45% decrease in patented drug list prices (Table 4). These price reductions are in the range of the PMPRB's own estimates of the average price reductions that will result from the proposed reforms.³⁷ They are meant to be illustrative; the price reduction for a given drug will depend on its treatment cost, unit sales and various other factors.

The 1-2 year models show that a 25% price decrease will result in an estimated 6-10% decrease in launch percentage for a given OECD country included in the model. Model 5, which is a 7-year model estimated with launch count data between 2011-2018, shows a 6% decrease in launch percentage with a greater degree of precision. All estimates show that the degree to which the launch percentage decreases is dependent on the price decrease. Our models suggest that the effect of price cuts on drug launch fractions is greater in the short-term than in the long-term, a result indicative of launch delays.

Table 4. Estimated percentage point decrease in expected launch percentage from a 25%, 35% and 45% decrease in list prices.

Price Decrease	Model 1 % (S.E.)	Model 2 % (S.E.)	Model 3 % (S.E.)	Model 4 % (S.E.)	Model 5 % (S.E.)
25%	10.666** [2.954]	6.273** [1.786]	7.750*** [1.988]	4.498* [1.919]	6.193*** [1.356]
35%	15.97** [4.424]	9.393** [2.675]	11.606*** [2.977]	6.736* [2.874]	9.273*** [2.032]
45%	22.163** [6.140]	13.036** [3.712]	16.106*** [4.132]	9.348* [3.989]	12.870*** [2.820]
N	29 [†]	31	31	31	30 [‡]

* p<0.05, ** p<0.01, *** p<0.001

†Launch Data for Greece and Turkey not available

‡Launch Data for Slovakia was not available

Estimated Standard Errors in parentheses

Discussion

The Government of Canada plans to implement new controls on both the list and actual transaction prices of patented drugs in January 2021.¹⁵ The literature indicates that controls on drug list prices delay drug launches.^{17-19,29,36} The Government's unpublished analysis concludes that the new price controls will not result in any launch delays.²⁷ It is possible that the results of the extant literature no longer apply. The literature uses data that is now almost 20 years out of date, drawn mostly from the 1990's.

Given these conflicting findings, we re-examine the issue empirically. Using recent OECD country level data, we estimate regression models of country level drug launches as a function of public list prices, market size and membership within the EMA. The models show that price is a particularly important covariate, and the impact of price on drug launch across this group of countries is greater in the short term than the long term, indicating that drug price controls will lead to drug launch delays. Though our methods and data sources differed, these findings are in alignment with previous studies on this topic.

If our results are correct, the degree to which launches will decrease in Canada will be determined by the magnitude of price decreases after the new PMPRB regulations are implemented in January 2021. Here, we predict that a 25% price decrease will lead to a 6-10% and 6% decrease in drugs launched over 1- and 8-year periods, respectively. Moreover, a 45% price decrease will lead to a 13-22% and 13% decrease in drugs launched over these respective periods. The estimates from the 8-year model also suggests that after a drug list price decrease, some drugs will likely not launch in Canada.

The welfare implications of reduced or delayed access depends on the therapeutic novelty of the drugs whose launch into Canada is delayed or prevented. Delays in access to therapeutically important new drugs will harm some Canadian patients.

However, most drugs currently entering the Canadian market are “me-too” drugs. From the period of 2010-2018, the PMPRB reports that 5% of 811 drugs evaluated by its Human Drug Advisory Panel were categorized as either a breakthrough drug (2.3%) or a drug offering a substantial improvement over other medicines in Canada (2.7%).⁴ The remaining drugs were either a moderate improvement (12.1%) or a “me too” drug, offering slight or no improvement to therapeutic gains achieved by current medicines on the market (82.9%).⁴ Delays in the launch of “me-too” drugs are unlikely to have appreciable effects on health outcomes. However, they may increase drug plan costs. The reason is that under standard health technology assessment procedures used in Canada, new drugs gain formulary coverage either by producing additional health gains at an acceptable price or by generating the same health gains as existing drugs but at a lower price. If such drugs are not launched, then drug plans will be unable to exploit the potential for cost savings.

The results of this paper need to be interpreted in light of several limitations. First, the outcome variable we focussed on – the fraction of drugs launched globally that are introduced into a country within a given period of time – does not directly address the length of the delay resulting from reductions in drug list prices. Second, the drug launch percentages were all calculated from aggregate data. As such, the models do not provide insight into the differences of impact that these price controls will have on different therapeutic classes of drugs. As discussed above, the domestic health impacts of launch delays will be determined by the therapeutic novelty of the drugs launched globally after January 2021 – something our models cannot predict. Third, like any observational study there is a risk of confounding variables. Characteristics of countries, drugs and pharmaceutical firms – for example patent protection, therapeutic class, and head office location respectively – that influence the launch timing of drug i in country j , could be correlated with price.¹⁷⁻¹⁹

A final limitation of these models is that they reflect the impact of variation in public list prices on launch fractions but not the actual transactions prices. This too will limit the predictive ability of our models. It is possible that particularly large reductions in actual transactions prices may cause delays that are larger than those predicted by the model. These limitations can be addressed by examining detailed data on the drugs that are launched into Canada once the PMPRB regulatory changes come into effect.

References

1. PMPRB. Mandate and Jurisdiction. 2018; Available at: <http://www.pmprb-cepmb.gc.ca/about-us/mandate-and-jurisdiction>. Accessed 01/30, 2019.
2. Zhang R, Martin D, Naylor CD. Regulator or regulatory shield? The case for reforming Canada's Patented Medicine Prices Review Board. *CMAJ* 2017;189(14):E515-E516.
3. PMPRB. Guidelines Modernization. 2016; Available at: http://www.pmprb-cepmb.gc.ca/CMFiles/Consultations/DiscussionPaper/PMPRB_DiscussionPaper_June2016_E.pdf. Accessed 03/04, 2019.
4. PMPRB. Annual Report 2018. 2018; Available at: <https://www.canada.ca/content/dam/pmprb-cepmb/documents/reports-and-studies/annual-report/2018/PMPRB-annual-report-2018-en.pdf> Accessed 07/23, 2020
5. PMPRB. Annual Report 2017. 2017; Available at: http://www.pmprb-cepmb.gc.ca/CMFiles/Publications/Annual%20Reports/2018/2017_Annual_Report_Final_EN.pdf Accessed 08/10, 2019
6. PMPRB. Annual Report 2016. 2016; Available at: http://www.pmprb-cepmb.gc.ca/CMFiles/Publications/Annual%20Reports/2017/2016_Annual_Report_Final_EN.pdf Accessed 08/10, 2019
7. PMPRB. Annual Report 2015. 2015; Available at: http://www.pmprb-cepmb.gc.ca/CMFiles/Publications/Annual%20Reports/2015/2015_Annual_Report_Final_EN.pdf Accessed 08/10, 2019
8. PMPRB. Annual Report 2014. 2014; Available at: http://www.pmprb-cepmb.gc.ca/CMFiles/Publications/Annual%20Reports/2014/2014_Annual_Report_Final_EN.pdf Accessed 08/10, 2019
9. Person U, Jonsson B. The end of International Reference Pricing System? *Appl Health Econ Health Policy*. 2016: 14:1-8
10. Government of Canada. A prescription for Canada: Achieving Pharmacare for All. *Final Report of the Advisory Council on the Implementation of National Pharmacare*. June 2019. Available at: <https://www.canada.ca/content/dam/hc-sc/images/corporate/about-health-canada/public-engagement/external-advisory-bodies/implementation-national-pharmacare/final-report/final-report.pdf>. Accessed 02/17/2020
11. Blomqvist A, Grootendorst P. Canadian pharmacare, drug prices, and pharmaceutical R&D. mimeo. July 2020
12. Canada Gazette. Regulations Amending the Patented Medicines Regulations. 2017; Available at: <http://www.gazette.gc.ca/rp-pr/p1/2017/2017-12-02/html/reg2-eng.html>. Accessed 12/22, 2018.
13. PMPRB. Steering Committee on Modernization of Price Review Process Guidelines. 2019; Available at: <http://www.pmprb-cepmb.gc.ca/view.asp?ccid=1378&lang=en>. Accessed 02/19, 2020.
14. PMPRB. PMPRB Guidelines 2019. Available at: <https://www.canada.ca/content/dam/pmprb-cepmb/documents/consultations/draft-guidelines/draft-guidelines-en.pdf>. Accessed 01/30 2019

15. PMPRB Draft Guidelines 2020. Available at: <https://www.canada.ca/en/patented-medicine-prices-review/services/consultations/draft-guidelines.html#summary-details1>. Accessed 30/6/2020
16. Strategic Policy Brand - Health Canada. Amendments to the Patented Medicines Regulations. Patented Medicine Prices Review Board Modernization. Cost-Benefit Analysis. Published September 08 2017
17. Cockburn IM, Lanjouw JO, Schankerman M. Patents and the Global Diffusion of New Drugs. *Am Econ Rev* 2016;106(1):136-164.
18. Kyle MK. Pharmaceutical Price Controls and Entry Strategies. *Rev Econ Stat* 2007;89(1):88-99.
19. Danzon PM, Epstein AJ. Effects of regulation on drug launch and pricing in interdependent markets. *Advances in health economics and health services research* 2012;23:35-71.
20. Mohamed O, Kreling DH. The impact of a Pricing Policy Change on Retail Prices of Medicines in Egypt. *Science Direct Value in Health Regional Issue*. 2016;10(C):14-18
21. MOHP (Ministry of Health and Population) (2012) Decree 499/2012 on pricing of human pharmaceutical preparations. *Official Gazette* (153), 3 July 2012
22. Holtorf, AP, Gialama F., Wijaya KE, Kalo Z. External Reference Pricing for Pharmaceuticals – A Survey and Literature Review to Describe Best Practices for Countries with Expanding Healthcare Coverage. *Science Direct Value in Health Regional Issue*. 2019:122-131
23. Ruggeri K, Nolte E. Pharmaceutical Pricing: The Use of External Reference Pricing. *Rand Health Quarterly* 2013;3(2):6
24. Federal Register. Medical Program; International Pricing Index Model for Medicare Part B Drugs. Available at: <https://www.federalregister.gov/documents/2018/10/30/2018-23688/medicare-program-international-pricing-index-model-for-medicare-part-b-drugs>. Accessed 02/02/2020
25. Reuters. Trump Signs Order to Lower Prescription Drug Prices. *New York Times*. Published July 24 2020. Available at: <https://www.nytimes.com/reuters/2020/07/24/us/24reuters-usa-trump-drugprices.html?searchResultPosition=2> Accessed 28/07/2020
26. Lambert L. Democrats pass U.S. bill to lower drug prices that Trump threatens to veto. *Reuters*. Published December 12 2019. Available at: <https://www.reuters.com/article/us-health-congress-pharmaceuticals/democrats-pass-us-bill-to-lower-drug-prices-that-trump-threatens-to-veto-idUSKBN1YG2EL> Accessed 28/07/2020
27. Regulatory Impact Analysis Statement. *Canada Gazette, Part II* 153:17. Published August 8 2019. Available at: <http://canadagazette.gc.ca/rp-pr/p2/2019/2019-08-21/html/sor-dors298-eng.html>. Accessed 12/12/2019
28. Kyle MK. The Role of Firm Characteristics in Pharmaceutical Product Launches. *Rand J Econ* 2006;37(3):602-618.
29. Danzon PM, Wang YR, Wang L. The impact of price regulation on the launch delay of new drugs—evidence from twenty-five major markets in the 1990s. *Health Econ* 2005;14(3):269-292.

30. NPDUIS. Meds Entry Watch 2016. 2016; Available at: http://www.pmprb-cepmb.gc.ca/CMFiles/NPDUIS/NPDUIS_MedsEntryWatch_2016_e.pdf. Accessed 02/02/2020
31. NPDUIS. Meds Entry Watch 2017. 2017; Available at: http://www.pmprb-cepmb.gc.ca/CMFiles/NPDUIS/NPDUIS_MedsEntryWatch_2017_e.pdf. Accessed 02/02/2020
32. NPDUIS. Meds Entry Watch 2018. 2018; Available at: <https://www.canada.ca/content/dam/pmprb-cepmb/documents/npduis/analytical-studies/meds-entry-watch/meds-entry-watch-2018-en.pdf>. Accessed 02/02/2020
33. Innovative Medicines Canada. An assessment of Canada's current and potential future attractiveness as a launch destination for innovative medicines. January 2019; Available at: http://innovativemedicines.ca/wp-content/uploads/2019/02/2019_01_29_-_IMC_PhRMA_LaunchSequencing_vFINAL3.pdf. Accessed 02/17/2020
34. Feenstra, Robert C., Robert Inklaar and Marcel P. Timmer (2015), "The Next Generation of the Penn World Table" American Economic Review, 105(10), 3150-3182; available at www.ggdcc.net/pwt. Accessed 08/01/2020
35. Zeukeng M, Seoane-Vazquez E, Bonnabry P. A comparison of new drugs approved by the FDA, the EMA, and Swissmedic: an assessment of the international harmonization of drugs. Eur J Clin Pharmacol 2018;74(6):811-818.
36. Danzon PM, Wang YR, Wang L. The impact of price regulation on the launch delay of new drugs – evidence from twenty-five major markets in the 1990s. Health Economics. 2005;14(3):269-292
37. PMPRB. Guideline Modernization: Case Studies. 2019; Available at: <http://www.pmprb-cepmb.gc.ca/view.asp?ccid=1419&lang=en>. Accessed 02/19, 2019

Supplementary Appendix

Section 1: Model Variants excluding observations from the USA and New Zealand.

Table S1: Parameter estimates of 1-2 year models excluding both the United States and New Zealand

Variable	Model 1 β (p-value)	Model 2 β (p-value)	Model 3 β (p-value)
log(price _i)	32.745* (0.050)	24.586* (0.013)	22.006* (0.041)
log(population _i)	6.142** (0.006)	5.774*** (0.001)	5.519** (0.005)
log(GDP _i /capita _i)	19.459* (0.012)	11.819* (0.042)	19.074** (0.007)
ema _i	13.505* (0.027)	14.644** (0.002)	7.930 (0.125)
Constant	-197.439* (0.019)	-124.844 (0.051)	-198.165* (0.010)
N	27 [†]	29	29
R ² adjusted	0.449	0.534	0.440

* p<0.05, ** p<0.01, *** p<0.001

†Launch Data for Greece and Turkey not available

Table S2: Parameter estimates of 7-8 year models excluding both the United States and New Zealand

Variable	Model 4 β (p-value)	Model 5 β (p-value)
log(price _i)	18.392 (0.059)	21.516** (0.001)
log(population _i)	6.767*** (0.000)	5.985** (0.002)
log(GDP _i /capita _i)	15.114* (0.017)	5.390 (0.452)
ema _i	12.663* (0.010)	10.038* (0.045)
Constant	-141.067* (0.041)	-12.305 (0.881)
N	29	28 [†]
R ² adjusted	0.490	0.582

* p<0.05, ** p<0.01, *** p<0.001

†Launch Data for Slovakia was not available

Table S3: Parameter estimates of 1-2 year models excluding the United States

Variable	Model 1 β (p-value)	Model 2 β (p-value)	Model 3 β (p-value)
$\log(\text{price}_i)$	31.005 (0.057)	23.868* (0.012)	20.198 (0.053)
$\log(\text{population}_i)$	6.648** (0.002)	5.960*** (0.000)	6.018** (0.001)
$\log(\text{GDP}_i/\text{capita}_i)$	20.080** (0.008)	12.085* (0.033)	19.739** (0.005)
ema_i	14.998** (0.010)	15.231*** (0.001)	9.561* (0.048)
Constant	-207.183* (0.012)	-128.876* (0.038)	-208.511** (0.006)
N	28 [†]	30	30
R ² adjusted	0.485	0.559	0.459

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

[†]Launch Data for Greece and Turkey not available

Table S4: Parameter estimates of 7-8 year models excluding the United States

Variable	Model 4 β (p-value)	Model 5 β (p-value)
$\log(\text{price}_i)$	17.258 (0.067)	21.358*** (0.001)
$\log(\text{population}_i)$	7.132*** (0.000)	5.946** (0.001)
$\log(\text{GDP}_i/\text{capita}_i)$	15.595* (0.013)	5.464 (0.434)
ema_i	13.803** (0.003)	9.898* (0.035)
Constant	-148.485* (0.028)	-13.039 (0.871)
N	30	29 [†]
R ² adjusted	0.525	0.634

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

[†]Launch Data for Slovakia was not available

Table S5: Parameter estimates of 1 year models excluding New Zealand

Variable	Model 1 β (p-value)	Model 2 β (p-value)	Model 3 β (p-value)
log(price _i)	37.906** (0.001)	22.124** (0.002)	27.955*** (0.000)
log(population _i)	6.149** (0.005)	5.701*** (0.001)	5.727** (0.003)
log(GDP _i /capita _i)	19.513* (0.010)	11.939* (0.037)	18.893** (0.007)
ema _i	13.620* (0.023)	14.824** (0.001)	7.441 (0.143)
Constant	-196.783* (0.017)	-126.731* (0.044)	-194.767* (0.011)
N	28 [†]	30	30
R ² adjusted	0.654	0.634	0.659

* p<0.05, ** p<0.01, *** p<0.001

[†]Launch Data for Greece and Turkey not available

Table S6: Parameter estimates of 7-8 year models excluding New Zealand

Variable	Model 4 β (p-value)	Model 5 β (p-value)
log(price _i)	16.258* (0.025)	21.653*** (0.000)
log(population _i)	6.681*** (0.000)	6.000** (0.001)
log(GDP _i /capita _i)	15.122* (0.015)	5.372 (0.443)
ema _i	12.795** (0.008)	9.990* (0.037)
Constant	-141.660* (0.036)	-11.944 (0.882)
N	30	29 [†]
R ² adjusted	0.582	0.682

* p<0.05, ** p<0.01, *** p<0.001

[†]Launch Data for Slovakia was not available

Section 2: Assessing Robustness of multi-year model

Table S7. Robustness Check of Model 4. Parameter estimates for $Launch \%_i$ are recalculated using single year data of covariates from 2014-2017, the time frame for which data is available. Model 4, also reported, uses the average of these 4 years for each estimate.

Variable	2014 Data β (p-value)	2015 Data β (p-value)	2016 Data β (p-value)	2017 Data β (p-value)	Model 4 β (p-value)
$\log(\text{price}_i)$	14.647* (0.039)	16.722* (0.022)	16.482* (0.021)	14.138* (0.034)	15.636* (0.027)
$\log(\text{population}_i)$	7.266*** (0.000)	6.919*** (0.000)	6.924*** (0.000)	7.121*** (0.000)	7.048*** (0.000)
$\log(\text{GDP}_i/\text{capita}_i)$	16.761** (0.007)	15.636** (0.009)	14.386* (0.018)	15.512* (0.013)	15.579* (0.011)
ema_i	14.767** (0.001)	13.597** (0.003)	13.661** (0.003)	13.356** (0.004)	13.855** (0.002)
Constant	-160.881* (0.016)	-148.349* (0.021)	-135.905* (0.039)	-149.140* (0.027)	-148.612* (0.025)
N	31	31	31	31	31
R^2 adjusted	0.615	0.613	0.608	0.594	0.609

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Section 3: Price Prediction Calculation

Model Equation:

$$Launch \%_i = \beta_0 + \beta_1 \log(price_i) + \beta_2 \log(population_i) + \beta_3 \log(regpop_i) + \beta_4 \log(GDP/capita_i) + \varepsilon$$

Where $Launch \%_i = y$ and $\log(price_i) = \log(x)$, it follows that:

$$\frac{dy}{d\log(x)} = \beta_1$$

Where for small changes in x ,

$$d\log(x) \cong dx$$

And dx is the change in x relative to the baseline value of x . Thus $\frac{dy}{dx} \cong \beta_1$ the absolute change in y per unit of proportional change in x . To determine the effect on y from a percentage change in x , we multiple dx by 100:

$$\frac{dy}{100 * d\log(x)} = \frac{\beta_1}{100}$$

Using this property, calculations for 25%, 35% and 45% drops in $price_i$ were performed to predict the resulting decrease in $Launch \%_i$

Section 4: Breusch-Pagan Test Results

Table S8: The Breusch-Pagan tests for homoskedasticity are not rejected at conventional levels in any of the models.

Variable	Model 1	Model 2	Model 3	Model 4	Model 5
$\chi^2(4)$	3.42	5.49	2.46	5.29	5.08
p-value	0.4898	0.2409	0.6514	0.2589	0.2788

Section 5: White-Huber Standard Errors

Table S8: The $\log(\text{price}_i)$ regression estimates for all models with White-Huber standard errors in parenthesis.

Variable	Model 1	Model 2	Model 3	Model 4	Model 5
	β [SE]	β [SE]	β [SE]	β [SE]	β [SE]
$\log(\text{price}_i)$	37.071** [7.700]	21.805** [3.529]	26.940*** [5.700]	15.636* [3.464]	21.527*** [3.705]

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$