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Effect of amended Patented Medicine Regulations on industry decisions to launch new drugs in Canada

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ABSTRACT: Over the past five years, Canada's federal government has attempted to force through radical changes to the regulations of the Patented Medicine Prices Review Board (PMPRB), the quasi-judicial agency that has performed its role of preventing time-limited drug patents from being abused for the last 35 years. Legal challenges led to the federal Cabinet cancelling most of the changes. The only one retained is in the PMPRB's external reference pricing test, where Switzerland and the United States will be replaced by six countries with generally lower list prices, which came into effect on July 1st, 2022. The government has said that, for the next few months, the "status quo" will be maintained, but how the amended regulations and guidelines will work subsequently is unknown. The objective of this article is to assess what the change in comparator countries might mean by using a case study of a highly-specialized, rare disease medicine approved in Canada within the last five years. The results are considered from the perspective of a global pharmaceutical executive in Europe or the United States deciding whether it is sensible from a business perspective to launch a similar innovative medicine in Canada in the next 12 to 18 months. Our global pharmaceutical executive faces a set of complex and difficult questions. The most fundamental are: will the PMPRB use its external reference pricing test with the new countries in the same way as it has in the past, and will the company's target list price that would be compliant using the old reference pricing test be compliant under the new rules? With so much unknown, the executive's decision seems highly likely to be wait-and-see. If companies commonly make this decision, launches of new medicines in Canada will, at best, be delayed and, at worst, not happen. Canada's attractiveness as a marketplace for new medicines has already diminished as a result of uncertainty about the PMPRB changes; the uncertainty will persist while new guidelines are drafted. Canadians need the PMPRB to become more creative and adaptable in setting maximum prices to encourage developers to launch new medicines in Canada. Further delays in access or complete denials of access to innovative drugs will hurt even more Canadians with unmet or poorly met health needs that could be helped by these medicines.

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INTRODUCTION

The Patented Medicine Prices Review Board (PMPRB) is the federal tribunal whose role is to prevent time-limited drug patents from being abused.[1] It has performed this role for the last 35 years. However, over the past five years, Canada's federal government has attempted to force through radical changes to the regulations of the PMPRB.

The PMPRB has used an external reference pricing test in which a company's intended list price for a new patented medicine in Canada is compared with list prices in seven other countries (France, Germany, Italy, Switzerland, Sweden, the United Kingdom and the United States). These countries are known as the PMPRB7.

An advisory panel provides the PMPRB with scientific advice on new patented medicines and categorizes them as breakthrough, substantial improvement, moderate improvement, or slight/no improvement. A medicine is considered to be a breakthrough only if it is "the first one sold in Canada to effectively treat a particular illness or to effectively address a particular indication."[2] Between 2011 and 2020, less than 3% of new patented medicines were classed as a substantial improvement and even fewer were considered to be a breakthrough.

When a new medicine is categorized as a breakthrough, the maximum price allowed was the median of prices in the PMPRB7,[3] while that for a substantial improvement medicine was the higher of the median of PMPRB7 prices and the top price of drugs in the same therapeutic class in Canada. Additionally, at no time can the Canadian price of any patented medicine, regardless of its therapeutic classification, exceed the highest corresponding price among the PMPRB7.

Original Planned Changes to the PMPRB

Under regulations first proposed in 2017, Switzerland and the United States, countries with generally higher drug prices, will be replaced in the reference pricing test by six countries that, on average, have lower list prices. They are Australia, Belgium, Japan, Netherlands, Norway and Spain. The new set of countries are the PMPRB11.

In addition, the PMPRB was to use new factors to regulate prices: (a) health technology assessments (a use for which they are not intended), and (b) tests based on Canada's per capita gross domestic product and the magnitude of the drug's sales in Canada. Manufacturers would also have been compelled to report confidential information about rebates negotiated with insurers to the PMPRB.

The planned changes would have converted the PMPRB into a price setter, rather than a patent abuse watchdog, and the prices of new medicines in Canada drastically reduced to a level that would have been unsustainable for drug developers. This situation caused much uncertainty among drug developers and concern among patients.

However, legal challenges led to the Quebec Court of Appeal and the Federal Court of Appeal striking down the use of health technology assessments and the other economic factors to set prices and the requirement to reveal business secrets.[4] The Federal Court of Appeal also found that the PMPRB had abused its existing powers.[5] The Supreme Court of Canada saw no merit in reviewing the Appeal Court's unanimous decision and the federal Cabinet chose not to risk further rejections when it announced in April that most of the PMPRB revisions are cancelled.[6] Only the change in comparator countries replacing the PMPRB7 with the PMPRB11 was implemented on July 1st, 2022.

Amended Changes to the PMPRB

The only information about how the PMPRB will proceed after July 1st has been a "Proposed Interim Guidance" released on June 30th, which stated that the PMPRB will adopt a "status quo" approach to carrying out its mandate.[7] No price reviews or investigations of new patented medicines will be conducted until new guidelines come into effect. The PMPRB expects to begin consulting on new guidelines in September with the intention of having a final set of guidelines in place by the end of 2022. However, past experience suggests that this may be an optimistic timeline.

Drug developers will not know for some time whether the new external reference pricing test will work as previously or change in some way. The PMPRB has significant latitude in interpreting its regulations when creating new guidelines.

Using the PMPRB11 countries in the same way as the PMPRB7 to set the maximum list price in Canada, an analysis by the Parliamentary Budget Office (PBO) suggests that the change could lead to an overall 19% reduction in the list prices of medicines in Canada.[8] The PBO provided no insight as to how using the PMPRB11 might impact specific types of medicines.

OBJECTIVE

To assess what the change in comparator countries might mean for a highly-specialized breakthrough medicine, we present a case study using list prices for a rare disorder drug approved in Canada within the last five years, although its name is anonymized. We will call it Innocel, as in previous case studies.[9,10] Innocel is used as a first-line, life-long therapy for a severely debilitating rare genetic disorder. It is an effective treatment for the disorder for which there is no effective alternative and, therefore, classified as a breakthrough. Median list prices for Innocel based on the PMPRB7 and PMPRB11 countries are evaluated from the perspective of a global pharmaceutical executive in Europe or the United States deciding whether it is sensible from a business perspective to launch a similar innovative medicine in Canada in the next 12 to 18 months.

METHODS

Innocel list prices from the PMPRB7 and PMPRB11 countries were supplied by PDCI Market Access.[11] The actual prices of Innocel, after conversion into Canadian dollars, were adjusted upwards by a consistent small percentage and rounded to preserve the medicine's anonymity. The PMPRB's Compendium of Policies, Guidelines and Procedures states that the median is the simple average of the middle two prices when the medicine is sold in an even number of countries.[3] When the number of countries is uneven, the median should be the price of the country at the midpoint, but this is not specified in the Compendium. The list prices were used to calculate the median price for Innocel as should be done under the present regulations using the PMPRB7 and PMPRB11.

RESULTS

The adjusted current list prices per dose of Innocel in the PMPRB7 and the PMPRB11 countries converted to Canadian dollars are shown in Table 1. The prices range from $20,028 in Italy to $35,246 in the United States. Median prices were calculated using prices available from the three PMPRB7 countries at the time of the first sale of Innocel in Canada when it came under the PMPRB's authority and the six PMPRB7 and 10 PMPRB11 countries for which current prices of Innocel are available (Table 2).

Innocel's list price when first sold was $25,016 and it remains at this price today. Thus, the list price did not exceed the median of the prices in the three PMPRB7 countries available at the time of the first sale of Innocel in Canada ($25,527). However, the median of current list prices in the six PMPRB7 countries with available data is lower at $23,925 and the median of the prices in the 10 PMPRB11 countries with prices is not surprisingly – since the United States is excluded – even lower at $22,191.

Table 1: Current list prices in Canadian dollars per dose of Innocel

Country	Innocel price
France[a,b]	$22,191
Germany[a,b]	$22,085
Italy[a,b]	$20,028
Sweden[a,b]	Not available
Switzerland[a]	$25,659
United Kingdom[a,b]	$27,239
United States[a]	$35,246
Australia[b]	$21,634
Belgium[b]	$26,408
Japan[b]	$21,726
Netherlands[b]	$26,662
Norway[b]	$23,501
Spain[b]	$22,191

a: PMPRB7 country; b: PMPRB11 country

Table 2: Median and highest prices in Canadian dollars per dose for Innocel

Calculated from:	Median price	Highest price
PMPRB7 countries available at time of first Canadian sale	$25,527	$29,137
6 PMPRB7 countries today	$23,925	$35,246
10 PMPRB11 countries today	$22,191	$27,239

DISCUSSION

The PMPRB's role begins when a new patented medicine is sold for the first time in Canada whether paid for by public or private insurance or directly by a patient. By the time of the first sale, most drug developers have a target Canadian list price in mind based on factors that include investments made in the drug's research and development program, costs of manufacturing, distributing and promoting the medicine, and any patient support program. Often the target price calculation would be performed by the Canadian affiliate in discussion with global headquarters, especially if any concern exists about international price referencing impacting prices attainable in other, potentially more profitable, countries. An assessment is made before the first sale in Canada to determine whether the target Canadian list price will be PMPRB-compliant. If it is, developers usually do not increase their price to the estimated PMPRB-regulated maximum price. If not, the manufacturer must decide whether to decrease its price to achieve compliance, keep the price and risk PMPRB action against the company, delay launching in Canada or not launch at all.

The price of Innocel at the time of the first sale was PMPRB-compliant, but its current price is not PMPRB11-compliant by at least 12.8%. This may not seem a large percentage, but it may be sufficient to deter a manufacturer from launching a new medicine in this country. The extent to which a developer's target Canadian price is below the PMPRB7 median but above the PMPRB11 median will make the difference between deciding whether to launch in Canada or not.

Our global pharmaceutical executive in Europe or the United States deciding whether it is sensible from a business perspective to launch an innovative medicine in Canada in the next 12 to 18 months faces a set of complex and difficult questions. The most fundamental is: will the PMPRB use its external reference pricing test with the PMPRB11 in the same way as it has used the PMPRB7?

This includes whether the scientific advisory panel will continue or further narrow its limited assessment of the relative benefits of new patented medicines or become more creative in its assessments. If even fewer medicines are classified as scientific advances, the prices that can be charged for them will be more restricted. This will discourage developers from launching innovative drugs in Canada, which will negatively impact patients' access to these medicines.

Excluding the United States, where medicines are commonly launched first, may mean that even fewer comparator prices are available when a drug is first sold here if Canada is still considered a priority market. What will the PMPRB do then, especially with first-in-class drugs? The uncertainty around prices over the past five years has led to delays in launching new medicines in Canada so that new drugs have been launched in other PMPRB11 countries before coming to Canada.[12] This is likely to persist given the vagueness around the interim guidance. As a result, developers may have launched in lower price PMPRB11 countries, which will mean their prices are now available for the Canadian reference pricing test. The use of these countries in the test has the potential to result in an even lower price ceiling in Canada than would have been the case earlier raising the likelihood that our pharmaceutical executive will decide not to launch the medicine here. With the uncertainties and delays over the last five years, Canadians may have missed the opportunity to access a cohort of beneficial drugs that will now never be launched here.

The PBO report found that Canadian list prices for many drugs diverge from the median of PMPRB7 prices.[8] The PBO believes that such divergence is, to some extent, the result of changes in exchange rates or because Canadian prices have increased with inflation, while prices in comparator countries have not. In the case of Innocel whose price is now above the median of the six PMPRB7 countries (Table 2), the difference is more likely due to the drug being launched initially in higher price PMPRB7 countries and then in lower price ones. Nevertheless, when the PMPRB initially sets a maximum price, it is only allowed

to vary in line with inflation. In other countries, prices can be revised as the market evolves. The PBO believes that much of its estimated overall reduction of 19% in list prices using the PMPRB11 could be attained by placing greater emphasis on ensuring prices are no higher than the PMPRB7 median. Our pharmaceutical executive must be concerned about whether the new PMPRB guidelines will include a more rigid approach to setting the maximum price and whether they will allow the maximum to be revised regularly.

The PBO also reports that the use of the PMPRB11 is likely to impact some drug classes more than others, although it does not say which ones. The sequencing of the human genome has led to significant developments in treating rare disorders. These medicines are frequently costly because they are just as expensive – if not more so – to develop as drugs for common disorders and are priced to recover development costs. If the launch of a rare disorder drug is under consideration, our pharmaceutical executive will have to take account of the likelihood that prices of these medicines will be particularly reined in under the new rules. The cancellation of most of the proposed PMPRB revisions does not mean that the PMPRB and the federal government have abandoned their objective of reducing medicine prices in Canada.

Another issue for our executive to consider is whether the changes in Canada will impact the company's business in other countries, especially those that use Canada as a comparator in their own external reference pricing tests. Canada has become a reference for some developing countries, such as Brazil, South Africa, and Egypt.[8] These countries have much larger populations than Canada and, consequently, are important potential markets for new medicines that manufacturers will not want endangered.

Finally, the case study examines a new medicine, but what about existing drugs? How will the new rules deal with them? Will they be grandfathered in or will their prices be retrospectively reviewed and potentially decreased?

CONCLUSION

Our pharmaceutical executive's decision-making must consider many facets when deciding whether to launch the medicine in Canada and whether the company's price will be PMPRB-compliant both at launch and over the medicine's patent life. Uncertainty about how prices will be regulated not only at launch but subsequently makes the risk of launching untenable from both a financial and a corporate point of view until greater clarity about the new guidelines is available. As a result, it seems highly likely that our executive's decision will be to wait-and-see. If this is a common occurrence among manufacturers, launches of new medicines in Canada will, at best, be delayed and, at worst, not happen, which will impact all Canadians.

Canada's attractiveness as a marketplace for new medicines has already diminished[13] as a result of ever-increasing barriers to patient access[14] and uncertainty about the PMPRB changes.[4] Canadians need the PMPRB and its scientific advisors to become more creative and adaptable in setting maximum prices to encourage developers to launch new medicines in Canada. Further delays in access or complete denials of access to innovative medicines will hurt even more Canadians with unmet or poorly met health needs that could be helped by these medicines.

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