



June 28, 2017

Attention: Patented Medicines Regulations Consultations
70 Colombine Driveway, Tunney's Pasture
Mail Stop 0910, Floor 10, Building Brooke Claxton Building
Ottawa, Ontario K1A 0K9

Dear Minister Philpott:

Enclosed, please find Hoffmann-La Roche Limited's (Roche Canada) response to the questions posed in Health Canada's public consultation document on *Proposed Amendments to the Patented Medicines Regulations*.

As you will note in our submission, we have provided feedback on each of the five areas of suggested changes to the current Patented Medicines Prices Review Board (PMPRB) regulations, but would like to provide our perspective on the broader topic of innovation, value and patient impact that form the cornerstone of our company's commitment to Canadians.

Founded on the principles of innovation and collaboration, Roche prides itself on leading the science and advancing the medical community's understanding of the pathology of disease and its response to medicines. We recognize this mission depends on the long-term sustainability of our healthcare system, which ultimately provides patients with access to our innovation. Roche plays an active role within our healthcare system and we are keen to partner with all relevant stakeholders to help build a system that is not only fair, but effective and efficient; a system that is built for the needs of Canadians today and tomorrow.

Creating a Funding System that Prioritizes the Health of Canadians

During her talk at the Economic Club of Canada luncheon on May 16th, 2017, Minister Philpott outlined a similar commitment to improving healthcare in Canada. While we agree that a focus on access, affordability and appropriate use of medicines will help to: (1) reduce health spending on medicines that offer little to no value above the established standards of care, and (2) ensure our system is built for long-term sustainability; we fundamentally believe that a discourse about the value of innovation in the healthcare sector must not be marred by a singular focus on the cost of advancement and a desire to change the distributed approach by which medicines are funded in our country.

The current reimbursement framework in Canada is built on a pragmatic, step-wise approach, which offers the government various negotiation points starting with:

1. The assessment of whether the price of a new medicine is non-excessive through the PMPRB;
2. The opportunity to establish the cost-effectiveness of a medicine (*i.e.*, the clinical and societal impact the medicine will have in the real world) via the Canadian Agency for Drugs and Technologies in Health (CADTH) or *Institut national d'excellence en santé et en services sociaux* (INESSS);

3. An opportunity for the federal, provincial and territorial drug plans to further negotiate this price collectively through the pan-Canadian Pharmaceutical Alliance (pCPA); and
4. The added opportunity for each province to build their individual needs into a Product Listing Agreement (PLA) that ultimately enables a medicine to be funded by the public drug plans.

The current access framework in Canada has built-in checks and balances that allow the government and public drug plans to evaluate the price, value and patient impact of a medicine before it is reimbursed. Changing any one pillar of this framework will require a re-assessment of the entire process to ensure the system does not fail the interests and needs of patients and healthcare providers.

As such, it is our view that PMPRB should maintain its current role in ensuring that the price of medicines are not “excessive” in Canada based on a standardized assessment of international price comparator data. We do not believe that adding a cost-utility analysis into PMPRB’s decision criteria will benefit patients, as an evaluation of cost-effectiveness is already built into the process through CADTH. Compounding this assessment with an additional analysis upfront will create a system that will require longer review timeframes and will provide access to fewer and fewer medicines, negatively impacting the health of Canadians.

Research and Development: Sharing the Whole Story

We understand that governments and payers have the arduous task of managing a growing health budget and are looking for ways to reform our system with a focus on sustainability. This is driving their need to look at standards like the market size for a medicine, the Gross Domestic Product growth rate, and a comparison to a larger list of “comparable” countries. However, much of this dialogue is predicated on the belief that the pharmaceutical industry does not and has not invested sufficiently in research and development (R&D) in Canada to warrant the prices we charge. Our greatest concern with this logic is that current regulations that outline how we account for R&D expenditure do not recognize significant portions of our investment into Canada as “research and development”.

The Scientific Research & Experimental Development (SR&ED) Program, for example, specifically does not credit R&D investments made by the Global headquarters of Canadian subsidiaries of multi-national corporations like Roche. This is problematic as these investments fuel clinical trials, support partnerships with Canadian entities (*e.g.*, hospital institutions, academic centers, other Canadian businesses), provide grants, donations or research funding to hospital institutions, etc. In addition to the Global investments, the SR&ED Program also does not account for local investments into patient support programs (programs that help Canadians secure access to the medicines and diagnostics they require to live a healthy life), as well as grants and donations that support initiatives to improve access to information and services within our healthcare system.

We believe Canada has the ability to lead on a global stage by becoming a prime destination for clinical research and innovative medicines. While a focus on affordability is important, it must not be viewed with a narrow lens and must not erode our collective commitment to build a system that responds to the needs of every Canadian.

Valuing Medicines

As is evident in our discussion on value, and as we noted in our response to PMPRB through its consultation in October 2016, Roche recommends and has adopted a pricing strategy, which aims to balance the needs of a manufacturer with those of patients, their care teams, as well as other local

stakeholders. Roche believes that it is appropriate to consider a number of key factors that reflect the value of innovative medicines, while keeping health system sustainability at the forefront. These factors include:

Degree of unmet medical need

The value of a medicine should take into account the impact the disease has on patients, their caregivers, as well as society. This includes evaluating the prognosis of the patient, severity of the disease, its impact on a patient's quality of life and his/her family, as well as the incidence and prevalence of the disease. It is also appropriate to evaluate what other treatment options (if any) are available; how effective they are; and how satisfied patients are with these existing options.

The science

The value of a medicine should consider the degree to which a manufacturer has developed innovative medicines that improve patient outcomes compared to the current standard of care.

Patient impact

It is appropriate to consider the resources required for the administration of our medicines, such as staff time, equipment, material investments, special premises, as well as any potential need for additional medicines, interventions, procedures or hospital stays. The value of a medicine should also look at the healthcare costs that may be saved as a result of using a particular medicine.

Societal impact

The value of a medicine should also consider the extent to which medicines allow patients and caregivers to go back to work and/or resume their roles within their families, thus returning key resources to society.

Quality of evidence

The quality of evidence a medicine brings with it is an important factor. It is relevant to consider the extent to which a company has engaged with external stakeholders, regulatory bodies, pricing and reimbursement authorities, as well as patient organizations, in designing its clinical trials, in an effort to address their evidence expectations around populations, endpoints and comparators. The number and size of trials, the methodology and homogeneity of the results and the representativeness of the patient population are crucial factors for the generation of robust evidence.

The pricing context

The value of a medicine should also include an evaluation of the external environment in which the new medicine will be used. Factors such as the price of potential comparators or analogues, the results of cost-effectiveness analyses, the potential impact the new medicine may have on healthcare budgets, as well as the affordability levels across countries are all relevant.

We hope you find our submission helpful in your review of the Patented Medicines Regulations. In addition, we encourage you to consider the Innovative Medicines Canada and BIOTECanada responses to this consultation, both of which we support. We look forward to your feedback and would welcome a dialogue about the perspectives we have shared both in this letter and within our formal response.

Regards,



David Shum
Director, Market Access & Pricing
Hoffmann-La Roche Limited
Phone: 905-542-5783
Fax: 905-542-5825
Mail to: david.shum@roche.com
www.rochecanada.com

Proposal #1: Introducing new factors to help determine whether a price is excessive

It is proposed that the Regulations be amended to include the following three new factors for consideration, under s. 85(1), when determining whether a medicine is being or has been sold at an excessive price:

- i. The pharmacoeconomic evaluation for the medicine and other medicines in the same therapeutic class in Canada and in countries other than Canada;
- ii. The size of the market for the medicine in Canada and in countries other than Canada; and
- iii. Gross Domestic Product in Canada.

1. Do you agree that a pharmacoeconomic evaluation is an important factor for the PMPRB to consider when determining whether a drug is priced excessively? If so, how should the evaluation be considered?

Roche recommends pharmacoeconomic evaluations remain a consideration of resource allocation for the health technology assessment (HTA) organizations, and not a factor for the PMPRB to consider when determining whether a drug is priced excessively. We believe that non-excessive pricing and willingness-to-pay should be treated as two separate concepts, with willingness-to-pay being assessed by budget holders and the non-excessive price evaluations by the PMPRB. There are a number of reasons why use of pharmacoeconomic evaluations should not be used by the PMPRB for price setting. These include:

- Pharmacoeconomic evaluations do not fit with the PMPRB's mandate
- Uncertainty is a key limitation of pharmacoeconomic evaluations
- Pharmacoeconomic evaluations are already a component of the Canadian access process

The following text elaborates on each of these topics.

Pharmacoeconomic evaluations do not fit with the PMPRB's mandate¹

The PMPRB's regulatory mandate is to ensure that a patentee is not abusing its patent rights by charging an excessive price. A pharmacoeconomic evaluation does not provide any insight into whether a price is excessive. Instead, it is a method used to answer the question of whether one intervention is a more efficient (*i.e.*, cost-effective) use of resources compared to other interventions. Therefore, using an analysis to determine efficiency is not equivalent to determining whether a price is excessive.

¹ This section will limit its discussion to the list price and not the net price. That is because CADTH and INESSS conduct its assessment of cost-effectiveness using the list price.

If the PMPRB is attempting to discriminate interventions into categories using the incremental cost-effectiveness ratio (ICER), Appendix A discusses the issues of using rigid thresholds in decision making. However, the use of thresholds, even at face value, would not support the PMPRB's ability to discriminate prices that are excessive from those that are not for another reason: the threshold is an output, the result of many different inputs.²

Uncertainty is a key limitation of pharmacoeconomic evaluations

Unlike the existing Section 85(1) and 85(2) factors that are used to assess whether a medicine has been sold at an excessive price in any market in Canada, a high degree of uncertainty is associated with the ICERs that come from pharmacoeconomic evaluations. The Canadian HTA bodies, CADTH and INESSS, typically make changes to the input parameters of pharmacoeconomic models and then report ranges of ICERs. They may estimate the ICER to be different due to a number of factors, none of them being price. CADTH and INESSS tend to use this as evidence of uncertainty. Adoption of a highly variable computed ratio to determine excessive pricing in Canada will reduce confidence in the PMPRB's decisions.

Pharmacoeconomic evaluation in Canadian access process

Pharmacoeconomic evaluations are *already* considered in the Canadian review process for new drugs. CADTH and INESSS (and insurance companies) are the appropriate organizations to estimate ICERs as this falls within their existing mandates. The pCPA, with membership from all regional drug plans, is the appropriate organization to discuss market size, affordability, predictability and implementation, among other things, and how they should influence price and access. It is able to use pharmacoeconomic evaluations to aid in decision-making; however, these evaluations are not the only item considered during negotiations with manufacturers. Ultimately, public and private payers are the appropriate organizations to assess individual budget, implementation and administration and how they relate to individual price and access.

2. Do you agree that the size of the market for the drug in Canada and other countries is an important factor for the PMPRB to consider when determining whether a drug is priced excessively? If so, how should the size of the market be considered?

Value is the key determinant of whether or not a drug is excessively priced. The size of the population should not be a consideration. For example, an undifferentiated product should not be expected to command a premium price regardless of whether the population served is small or large; the price should be driven by the benefit offered to patients.

² Examples of inputs include: time horizon, dose intensity, length of stay following a Grade 4 adverse event, cost of a MRI, frequency of outpatient visits, quality of life data source, utility weighting algorithm, and choice of extrapolation method.

3. Do you agree that Canada's GDP and GDP growth are important for the PMPRB to consider when determining whether a drug is priced excessively? If so, how should GDP be considered?

Roche agrees that GDP has a place in the assessment of drug prices. Specifically, we support the use of GDP to help determine the appropriate basket of countries against which Canadian prices should be compared when performing international reference pricing (IRP). Once the basket is determined based on appropriate macroeconomic indicators, IRP can be used to determine whether a drug is priced excessively.

The PMPRB provided no details on its proposed vision and implementation of using GDP growth to regulate whether a price is excessive. We can only surmise that the PMPRB is suggesting using GDP growth in a similar or complementary way to the way it uses the consumer price index (CPI). We acknowledge that it is possible to use it to assess price changes; however, it is Roche's position that using CPI represents a better metric for monitoring price changes. The CPI is a more direct and exclusive measure of general price changes. Use of GDP growth could be overly sensitive to changes in commodity prices; a factor to which Canada is particularly susceptible. As such, the PMPRB's current Regulations of drug price changes would not be enhanced with the addition of GDP and/or GDP growth rate.

4. Are there any other factors that should be considered by the PMPRB when determining whether a drug is priced excessively? How should the factor(s) be considered and what information should be required from patentees?

As noted in our previous response to the 2016 PMPRB Consultation and our provided cover letter, Roche believes that the following factors should be considered when determining the price of a medicine:

- *Degree of unmet medical need*
- *The science*
- *Patient impact*
- *Societal impact*
- *Quality of evidence*
- *The pricing context*

The first five of these six factors help to inform decisions regarding the level of therapeutic improvement a new medicine offers over its existing comparators. We believe that the level of therapeutic improvement should be a factor that is considered within the regulations for the assessment of excessive drug pricing. Inclusion of this assessment aligns with the PMPRB's current practices. In Section C.6 of the Compendium of Policies, Guidelines and Procedures (PMPRB Guidelines), the PMPRB identifies a number of factors that should be considered. These factors are presented in Table 1.

Table 1: Factors considered in the assessment of level of therapeutic improvement

Primary Factors	Secondary Factors
<ul style="list-style-type: none"> ● Increased efficacy ● Reduction in incidence or grade of important adverse reactions 	<ul style="list-style-type: none"> ● Route of administration ● Patient convenience ● Compliance improvements leading to improved therapeutic efficacy ● Caregiver convenience ● Time required to achieve the optimal therapeutic effect ● Duration of usual treatment course ● Success rate ● Percentage of affected population treated effectively ● Disability avoidance/savings

Although it has become standard practice for the PMPRB to use this approach in the assessment of non-excessive pricing, the need for therapeutic improvement to be included in the evaluation of excessive pricing is not explicitly included in the existing Regulations. As noted by Board Staff in its supplementary reply to the supplementary response to Board Staff's amended Statement of Allegations:

To the extent that Alexion relied upon "publications, practices and representations" of the Board, it did so at its own peril. The administrative steps taken by Board Staff in its review and investigation of the price of Soliris do not fetter the Hearing Panel in determining whether the price of Soliris is excessive. Such a determination can only be reached by application of the factors set out in s. 85(1) and (2) of the Act.¹

Given this, it is imperative that the additional factors noted by Roche be included in the Regulations to create a fair business environment for patentees.

Roche also believes that the level of competition should be considered when assessing whether a price is excessive, as this relates directly to the level of unmet need. To achieve this, the number of comparator products available should be considered. As monopoly power can only be leveraged in the absence of competition, omitting this factor limits the PMPRB's ability to prioritize the evaluation of products that are at risk of abusing their market power.

Proposal #2: It is proposed that the countries in the Schedule to the Regulations be revised as follows:

Current Schedule	Proposed New Schedule
<ul style="list-style-type: none"> • France • Germany • Italy • Sweden • Switzerland • United Kingdom • United States 	<ul style="list-style-type: none"> • Australia* • Belgium* • France • Germany • Italy • Japan* • Netherlands* • Norway* • South Korea* • Spain* • Sweden • United Kingdom

* New countries added to the list

5. Are there other countries that should be considered in revising the Schedule?

Roche agrees that a criteria-based approach is needed to determine which countries should be included as comparator countries. These criteria should be presented in the Regulations and used to define the countries that are included in the Schedule.

Within the consultation document, the following criteria were directly identified:

- **Consumer protection:** whether the country has national pricing containment measures in place to protect consumers from high drug prices;
- **Economic Standing:** whether the country has a similar economic standing to Canada, as measured by GDP per capita; and
- **Pharmaceutical market characteristics:** whether the country has similar market characteristics to Canada, such as population, consumption, revenues and market entry of new products.

In addition, the indirect criterion that the country must be a member of the Organisation for Economic Co-operation and Development (OECD) was also set given the government’s stated objective in its Health Canada consultation document to:

Update the list of countries used for price comparison so that it is more aligned with the PMPRB's consumer protection mandate and median OECD prices.²

Addition of Switzerland based on listed criteria

Based on Health Canada's stated criteria, Switzerland should be added to the Schedule. The way in which Switzerland meets these criteria is shown in Table 2. It is unclear what factor(s) prompted its removal from the list of new comparator countries.

Table 2: Assessment of Switzerland's applicability to the selection criteria for comparator countries

Criteria	Applicability
Consumer protection	International reference pricing is used to assess the acceptability of drug prices
Economic standing	<p>Switzerland's GDP per capita falls between those of Norway and Spain, both of which are on the list of future comparator countries.</p> <p>Like Canada, Switzerland is one of 11 member countries of the Group of 10 (G10). Nine of the 11 G10 countries (<i>i.e.</i>, Belgium, France, Germany, Italy, Japan, the Netherlands, Sweden, Switzerland, and the United Kingdom) are included in the proposed list of reference countries. The United States is the 11th member of the G10.</p>
Pharmaceutical market characteristics	The share of new active substances launched in Q4 2015 is between that of Canada and the OECD median. ³

Addition of United States based on listed criteria

Roche also believes that the United States should be included as a comparator country. Although the United States does not meet all of the criteria proposed in the consultation document, it is the international market that is most like Canada, given the significance of private market reimbursement in both countries. Like Canada, the United States is a member of the OECD, the Group of 7 (G7), the G10 and the G20. Operationally, other OECD countries (*i.e.*, Japan and South Korea) include the United States as a reference country, with both countries having foreign-to-Canadian price ratios for patented

drugs below that of Canada in 2015. Of note, the foreign-to-Canadian price ratio in South Korea of 0.50 is less than the median OECD ratio of 0.78, which demonstrates that inclusion of the United States as a reference country does not determine whether local prices will be among the highest internationally.⁴ Given this, it remains reasonable to include the United States as a comparator country.

6. Are there other criteria that should be considered in revising the Schedule?

Minister Philpott has publically stated that her priority is to make medicines more affordable, accessible and appropriately prescribed.⁵ As such, it is important that the criteria used to identify reference countries reflect these priorities. In its current form, it is unclear whether the proposed criteria achieve this objective.

Roche recommends that Health Canada further define how the inclusion/exclusion criteria will be used to create a new list of reference countries. This should include clarifying and expanding the methods of measurement being used to assess each criterion. A non-exhaustive list of possible complementary measurement options has been provided for consideration. Regardless of the criteria used, a clear algorithm specifying how the criteria are to be applied needs to be defined.

Table 3: Criteria for selection of comparator countries

Criterion	Method(s) of measurement proposed by Health Canada	Examples of complementary measurement options
Consumer protection	<ul style="list-style-type: none"> Existence of national pricing containment measures 	
Economic standing	<ul style="list-style-type: none"> GDP per capita Member of OECD 	<ul style="list-style-type: none"> Organized collaboration with Canada's economic peers (<i>e.g.</i>, Group of Seven) Net national wealth Level of development (<i>e.g.</i>, Human development index)
Pharmaceutical market characteristics	<ul style="list-style-type: none"> Population Consumption Revenues Market entry of new products 	<ul style="list-style-type: none"> National policies: Priority level of healthcare (<i>e.g.</i>, health expenditure as a percentage of GDP) Access to medicines (<i>e.g.</i>, number of products launched)

7. Please provide any other comments you may have on the Schedule of comparator countries.

Roche believes that Health Canada must first perform a robust assessment of how revising the list of comparator countries will impact Canada's access to life saving and life changing medicines and how the proposed changes will be operationalized before any changes are implemented. At present, it does not appear that such an evaluation has been performed to develop the proposed list. Questions that need to be considered include:

- How will the inclusion of four countries with access levels below that of Canada and the OECD median (*i.e.*, Australia, Japan, Netherlands and Korea) in the new group of reference countries affect access to innovative medicines in the future?
- Does pricing information available in all of the proposed countries comply with the PMPRB's established method of determining Foreign Price Sources?

In addition to considering these questions, Health Canada and the PMPRB need to determine whether use of international reference pricing following the launch of a new medicine achieves Health Canada's aim of moving to a risk-based approach with respect to Regulations and the PMPRB's regulatory framework. It is Roche's position that international reference pricing should only be used to assess the launch price of a new medicine.

Additional details concerning this question can be found in Appendix B.

Proposal #3: Reducing regulatory burden for generic drugs with a patent

It is proposed that the Regulations be amended to set out that patented generic drugs, which received market authorization from Health Canada through an Abbreviated New Drug Submission, be required only to report identity and price information in the event of a complaint or at the request of the Patented Medicines Prices Review Board.

1. Do you agree that patentees of generic drugs, i.e. drugs that have been authorized for sale by Health Canada through an ANDS should only report information about the identity of the drug and its price in the event of a complaint or at the request of PMPRB?

Roche agrees with the rationale presented in this paper and elsewhere that genericized products require less oversight versus those products that hold a monopoly. Roche is of the opinion that this same level of oversight should be expanded to include the innovator product once a generic version of the drug, a biosimilar of the drug or a comparator drug that uses the same mechanism of action as the innovator drug has been sold in Canada. This is aligned with the PMPRB's move towards a risk-based approach to regulation. As noted in the Health Canada consultation document:

[a] risk-based approach is proposed to guide amendments to the Regulations and the modernization of the PMPRB regulatory framework. Central to this approach is the recognition that patented drugs have differing potential to exert market power and charge excessive prices. This potential is largely shaped by the characteristics of the market for each drug, such as the availability of comparator products and the size of the patient population the drug is used to treat. *It is proposed that drugs be evaluated against such characteristics to determine their relative risk of excessive prices. Drugs with higher potential to exert market power would face a higher degree of regulatory scrutiny while drugs with medium or lower risk of excessive prices would face respectively lower oversight.* [Emphasis added]²

Proposal #4: Modernizing reporting requirements for patentees

It is proposed that the Regulations be amended to set out the information required to enable the PMPRB to consider the new factors as proposed:

- a. For the new factor – the pharmacoeconomic evaluation for the medicine and other medicines in the same therapeutic class in Canada and in countries other than Canada – the Regulations would be amended to require patentees to submit:
 - o the cost utility analysis by approved indication of the medicine, where that information is available to the patentee

This information would be as consistent as possible with the information required by CADTH's Common Drug Review, pan-Canadian Oncology Review and l'Institut national d'excellence en santé et en services sociaux (INESS).[sic]

- b. For the new factor – the size of the market for the medicine in Canada and in countries other than Canada – the Regulations would be amended to require the patentee to submit:
 - o the estimated uptake of the medicine, by approved indication, in Canada without restraint on utilization (e.g. market/budget impact analysis in any relevant market), where that information is available to the patentee

No information would be required from patentees on per capita GDP or growth in GDP.

1. Is the information sought in relation the new factors relevant and sufficient?

Roche is of the opinion that pharmacoeconomic evaluations, budget impact analyses, per capita GDP and growth in GDP are irrelevant with respect to the assessment of non-excessive pricing. This position has been described in detail in response to questions concerning Proposal #1.

It is also Roche's position that therapeutic improvement, as defined in Section C.6 of the current PMPRB Guidelines, should be added to the list of factors included in the Patented Medicines Regulations. Submission requirements for patentees should be consistent with current practices.

2. Is this information generally available to patentees?

As noted in the previous question, Roche is of the opinion that the information being requested is irrelevant when assessing non-excessive pricing. The Canadian information requested in Proposal #4 is not always available. As part of submissions to Canadian Health Technology Assessment (HTA) agencies (*i.e.*, CADTH, INESSS) and Federal/Provincial and Territorial drug plans, manufacturers may be required to submit pharmacoeconomic evaluations as well as budget impact analyses. For post-launch products, this information is not available due to the following reasons:

- the market or standard of care may have changed
- analyses may not have been performed/required
- comparator(s) may have changed in price or number.

It is not expected that international pharmacoeconomic evaluations or budget impact analyses will be generally available to Roche Canada for filing. Beyond our inability to obtain these evaluations, Roche does not recommend the use of cross-country comparisons as the evaluations for each country will incorporate country-specific factors (*e.g.*, practice patterns, incidence and prevalence data, healthcare costs) that may not be applicable to Canada.

Proposal #5: Providing information related to third party rebates

It is proposed that the Regulations be amended to require patentees to report to the PMPRB all indirect price reductions, given as a promotion or in the form of rebates, discounts, refunds, free goods, free services, gifts or any other benefit in Canada.

1. Are there any reasons why patentees should not be required to disclose to the PMPRB information on indirect discounts and rebates provided to third party payers?

Roche does not believe that patentees should be required to disclose to the PMPRB information on indirect discounts and rebates provided to third party payers. Based on the PMPRB consultation document and the Health Canada consultation, it appears that the purpose of having access to these data is to lower ex-factory list prices. Specifically, according to the Minister:

We're proposing a requirement to report rebates, discount & refunds to payers, which could help set a fairer price ceiling.⁵

Use of this information to establish price ceilings represents a poor policy choice for a number of reasons. First, from a competitive business standpoint, this approach carries significant risk as it uses confidential pricing information in a manner that could lead to its disclosure to third parties. Second, the use of these rebates and discounts to establish price ceilings may introduce incentives within the healthcare system that contradict the government's focus on improving access, affordability and appropriate use. Finally, it remains unclear how the PMPRB will overcome the logistical issues associated with regularly using these data to revise price ceilings. These challenges are explored below, with additional details being provided in Appendix C.

Challenges regarding confidentiality

Discounts and rebates provided to third party payers are negotiated and provided under explicit legal obligations of confidentiality, both on the part of the third party payer and on the part of the patentee. The expectation of confidentiality is critical to enabling the parties to arrive at mutually acceptable rebate/discount terms. Any regulations requiring the disclosure of such third party rebates and discounts would necessarily require adequate provisions to protect the confidentiality of this information.

At this stage, it is unclear exactly how this confidential information will be used by the PMPRB, and therefore it is difficult to provide precise feedback on the nature of protections that would need to be in place regarding confidential business information feedback. Should the third-party rebate/discount of a given product be used indirectly to reduce the list or net price of comparator products, this information could be used to back-calculate confidential rebates/discounts and therefore jeopardize confidentiality. Until such time that more information is available regarding the use the PMPRB intends to make of these third-party discounts/rebates, Roche cannot make a meaningful assessment of the risks associated with the sharing this information based on the information provided in the Health Canada consultation document. If appropriate due diligence is not performed prior to the introduction of

Proposal #5 to understand its impact, the implementation of this change could have serious local and global implications for the pharmaceutical industry and, in turn, patients.

Challenge of incentives

The proposed regulatory changes concerning the reporting of discounts and rebates, as well as the desire to use this information to lower drug ceiling prices, do not consider the level of patient access associated with indirect rebates or discounts. The level of access may be impacted by one of the following factors:

Reimbursement criteria: The reimbursement criteria required for a patient to have access to a medicine may differ between payers, with some having more restrictive criteria relative to other payers.

Administrative burden: The behavior of physicians can be impacted by the amount of administrative work required to prescribe a medicine relative to other treatment options.

At present, indirect rebates and discounts can be used to encourage payers to provide the broadest, most appropriate access to innovative medicines. If indirect rebates and discounts are used to bring down national price ceilings, all payers will receive the same net price. Under this scenario, payers wishing to control upfront costs (*i.e.*, the budget impact of adding a new medicine) will be incentivized to restrict patient access to achieve their desired outcome. It is important that the incentives created by changes to the Patented Medicines Regulations ensure that patients receive better access to medicines, as was noted by Minister Philpott. Not establishing price ceilings using indirect rebates and discounts helps to achieve this end.

Logistical Challenges

Application of Proposal #5 will result in invoice data being reported to the PMPRB more than a year after the initial sale of a medicine has occurred given that the frequency of invoicing is variable. In the absence of additional information on how indirect rebates and discounts will be used, it remains unclear how the PMPRB will be able to assess non-excessive pricing on an annual basis for all products if the true net price of the product cannot be assessed until up to two years after the initial transaction has taken place. This issue of timing must be thoroughly evaluated to assess whether this proposal is practical for mandatory reporting.

Additional considerations: Reporting of Research and Development

Roche believes that, with the amending of the Patented Medicine Regulations, now is the time to address issues concerning the estimation of the pharmaceutical industry's contribution to Canadian Research and Development (R&D). As stated in Section 6 of the current Patented Medicine Regulations:

For the purposes of subsection 88(1) of the Act, the expression research and development means those activities for which expenditures qualify, or would qualify if the expenditures were made by a taxpayer in Canada, for an investment tax credit in respect of scientific research and experimental development under the Income Tax Act as that Act read on December 1, 1987.

When the original Regulations were drafted, this definition of R&D appropriately reflected the way in which manufacturers conducted R&D. Since that time, the way in which investments are made by manufacturers has evolved. We encourage Health Canada to engage with industry to modernize the R&D formula for the 21st century while also creating Regulations that are flexible enough to adapt to the business models of the future. This is the only way that Canadians will obtain a true picture of R&D investments in Canada.

We recommend that, at a minimum, the following factors should be considered when reporting R&D investment:

- Investments made by Global headquarters of Canadian subsidiaries in Canada, including:
 - Investments in clinical trials
 - Partnerships with Canadian institutions, academics, and companies
 - Grants & donations to hospitals
- Other expenditures in Canada not included in SR&ED, including
 - Patient support programs
 - Grants & donations to healthcare related projects or institutions

References

1. PATENTED MEDICINE PRICES REVIEW BOARD IN THE MATTER OF the Patent Act, R.S.C. 1985, c. P-4, as amended AND IN THE MATTER OF Alexion Pharmaceuticals Inc. (the "Respondent") and the medicine "Soliris", BOARD STAFF'S SUPPLEMENTARY REPLY TO THE SUPPLEMENTARY RESPONSE TO BOARD STAFF'S AMENDED STATEMENT OF ALLEGATIONS. (Accessed June 27, 2017, 2017, at http://www.pmprb-cepmb.gc.ca/CMFiles/Hearings%20and%20Decisions/Decisions%20and%20Orders/supplementary_reply.pdf.)
2. Protecting Canadians from Excessive Drug Prices: Consulting on Proposed Amendments to the Patented Medicines Regulations. Health Canada, 2017. (Accessed June 27, 2017, 2017, at <https://www.canada.ca/en/health-canada/programs/consultation-regulations-patented-medicine/document.html>.)
3. Meds Entry Watch, 2015. Patented Medicine Prices Review Board, 2017. (Accessed June 27, 2017, 2017, at <http://www.pmprb-cepmb.gc.ca/view.asp?ccid=1307&lang=en#app1>, .)
4. Annual Report 2015. Patented Medicine Prices Review Board, 2016. (Accessed June 27, 2017, 2017, at <http://www.pmprb-cepmb.gc.ca/view.asp?ccid=1273>.)
5. Remarks from the Honourable Jane Philpott, Minister of Health, to the Economic Club of Canada – May 16, 2017. Health Canada, 2017. (Accessed June 27, 2017, 2017, at https://www.canada.ca/en/health-canada/news/2017/05/economic_club_ofcanada-may162017.html?=&wbdisable=true.)
6. Cost effectiveness and strategic planning (WHO-CHOICE). Table: Threshold values for intervention cost-effectiveness by Region. World Health Organization. (Accessed June 2017, at http://www.who.int/choice/costs/CER_levels/en/.)
7. McCabe C, Claxton K, Culyer AJ. The NICE Cost-Effectiveness Threshold. *Pharmacoeconomics* 2008;26:733-44.
8. Grosse SD. Assessing cost-effectiveness in healthcare: history of the \$50,000 per QALY threshold. *Expert review of pharmacoeconomics & outcomes research* 2008;8:165-78.
9. Claxton KM, Steve; Soares, Marta; Rice, Nigel; Spackman, Eldon; Hinde, Sebastian; Smith Peter C; Sculpher, Mark. Written evidence to the House of Commons Health Select Committee on the NICE cost-effectiveness threshold (NICE 61). 2013.
10. Hutubessy R, Chisholm D, Edejer TT-T. Generalized cost-effectiveness analysis for national-level priority-setting in the health sector. *Cost effectiveness and resource allocation* 2003;1:8.
11. Freedberg KA, Tosteson AN, Cotton DJ, Goldman L. Optimal management strategies for HIV-infected patients who present with cough or dyspnea. *Journal of general internal medicine* 1992;7:261-72.
12. Hirth RA, Chernew ME, Miller E, Fendrick AM, Weissert WG. Willingness to pay for a quality-adjusted life year in search of a standard. *Medical Decision Making* 2000;20:332-42.
13. Danzon PM, Towse A, Mulcahy AW. Setting cost-effectiveness thresholds as a means to achieve appropriate drug prices in rich and poor countries. *Health Affairs* 2011;30:1529-38.
14. Sculpher M, Claxton K, Pearson SD. Developing a value framework: the need to reflect the opportunity costs of funding decisions. *Value in Health* 2017;20:234-9.
15. Woods B, Revill P, Sculpher M, Claxton K. Country-level cost-effectiveness thresholds: initial estimates and the need for further research. *Value in Health* 2016;19:929-35.
16. Caro JJ. How relevant is cost-effectiveness anyway? *European heart journal* 2013;34:245-6.
17. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. *CMAJ: Canadian Medical Association Journal* 1992;146:473-81.
18. Baker R, Chilton S, Donaldson C, et al. Searchers vs surveyors in estimating the monetary value of a QALY: resolving a nasty dilemma for NICE. *Health Economics, Policy and Law* 2011;6:435-47.
19. Nimdet K, Chaiyakunapruk N, Vichansavakul K, Ngorsuraches S. A systematic review of studies eliciting willingness-to-pay per quality-adjusted life year: does it justify CE threshold? *PloS one*

2015;10:e0122760.

20. Vallejo-Torres L, García-Lorenzo B, Castilla I, et al. On the Estimation of the Cost-Effectiveness Threshold: Why, What, How? *Value in Health* 2016;19:558-66.
21. Investigating NICE's Cost Effectiveness Threshold. 2014. (Accessed Jun 2017, at <https://www.ohe.org/research/investigating-nices-cost-effectiveness-threshold>.)
22. Dakin H, Devlin N, Feng Y, Rice N, O'Neill P, Parkin D. The influence of cost-effectiveness and other factors on nice decisions. *Health economics* 2015;24:1256-71.
23. Donnelly L. Cameron pledges to lift restrictions on cancer drugs available on NHS. *The Telegraph* 2010.
24. Adams S. Head of Nice has regrets over drugs refusals. *The Telegraph* 2010.
25. Ramesh R. Emergency fund to pay for 'too expensive' cancer drugs. *The Guardian* 2010.
26. NICE. Appraising life-extending, end of life treatments. London: National institute for Health and Clinical Excellence; 2009.
27. Formulas for Foreign Price Verification. Patented Medicine Prices Review Board, 2017. (Accessed June 27, 2017, 2017, at <http://www.pmprb-cepmb.gc.ca/view.asp?ccid=502>.)

Appendices

Appendix A: Challenges with the use of ICER thresholds

Appendix B: Considerations for revision of list of comparator countries

Appendix C: Impact of the reporting of discounts and rebates to third party payers

Appendix A: Challenges with the use of ICER thresholds

Arbitrary thresholds do not support HTA decision making

The consultation paper states that the PMPRB could introduce a fixed cost-per-QALY threshold. Roche disagrees with using pharmacoeconomics to determine excessive pricing; Roche also disagrees with the adoption of a rigid cost-effectiveness threshold for HTA decision making. There are no thresholds with strong theoretical or evidence-based validity. Most thresholds, like the World Health Organization's threshold of 1-3 times per capita gross domestic product⁶, the National Institute for Health and Care Excellence (NICE)'s range of GBP 20,000-30,000/QALY⁷ and the standard USD 50,000/QALY⁸, used a lot in academia previously, were clearly cited as arbitrary⁸⁻¹². Arbitrary thresholds do not lead to legitimate decisions. This is something economists searching to identify a threshold have stated previously¹³⁻¹⁶.

In Canada, there has been no real methodological work to estimate the threshold. One of the most widely referenced works on a threshold was Laupacis' paper which defined thresholds by strength and quality of evidence¹⁷. However, even Laupacis admits that the thresholds he advocated were arbitrarily chosen.

Research into a credible explicit threshold is immature

Whilst it is theoretically possible to elicit societal preferences of a willingness-to-pay threshold¹⁸, many challenges remain. Studies that have attempted to elicit a threshold willingness-to-pay for a QALY have displayed heterogeneous methods and results^{19,20}. Heterogeneity arises from perspective^{19,20}, study population¹⁹, and health state. This heterogeneity in design and analysis can lead to heterogeneity in results and limited interpretation²⁰.

Elucidating willingness-to-pay is no small task and fraught with challenges. For this reason, CADTH and INESSS, do not identify an explicit threshold willingness-to-pay, instead using incremental cost effectiveness ratios as one input into HTA decision making. The PMPRB has not and does not conduct methodological research in this area. It would be deeply out of its expertise and mandate to hastily define and employ a rigid single threshold or threshold range that carried no real legitimate value.

Thresholds are arbitrary and arbitrary thresholds do not lead to legitimate decisions. The state of methodological research into a credible explicit threshold is immature globally, nonexistent in Canada and inadequate to support implementation.

Negative consequences when using rigid thresholds in HTA decision making

Few countries employ the use of rigid thresholds (which are all arbitrary numbers). In 2004, the UK, through NICE, employed a threshold of GBP 20,000-30,000/QALY⁷. In fact, to this date, cost-effectiveness remains *the* dominant consideration into funding recommendations from NICE, with almost no other variables having a significant effect on decisions²¹.

Given the explicit threshold, NICE refused patient access to a number of innovative treatments²². In particular, NICE refused access to a number of oncology drugs. This rationing based on the arbitrary threshold was challenging for the public and media to accept^{23,24}. Controversy ensued until, finally, in 2011, the NHS England capitulated and decided to formally introduce an exception to the threshold; an emergency fund called the Cancer Drugs Fund (CDF) would be made available to patients in order to

access oncology drugs rejected by NICE because of cost-effectiveness²⁵, a decision mainly driven by an ICER greater than the arbitrary threshold.

The CDF essentially undermined the HTA body's ability to render recommendations that were reflected in implementation. As well, the CDF budget eventually became unsustainable. Finally, in 2016, it underwent reform. The CDF is now positioned as pathway for coverage with evidence development and NICE now has the ability to recommend use within the CDF. At this point, it is too early to give a final verdict on what value the new CDF pathway provides patients and the healthcare system.

The history of the CDF, among many things, represents the failures of an arbitrary rigid threshold. A rigid arbitrary threshold led to decisions unacceptable by the public or government. The NHS eventually created an alternate fund that undermined the recommendations by NICE. The fund eventually grew out of control.

The CDF was not the only formal exception to the threshold. In 2009, NICE gave supplementary advice which introduced their end-of-life criteria²⁶, which allowed for consideration of interventions whose ICER exceeded GBP 30,000/QALY for patients with short life expectancy. Recognizing that medicines that address rare diseases may fail their arbitrary 2004 threshold, NICE also introduced their Highly Specialised Technology Evaluation Committee in 2013, a program which does not identify a rigid threshold.

Appendix B: Considerations for revision of list of comparator countries

Access concerns

The PMPRB's Med Entry Watch 2015 report provides OECD-level data regarding new active substances (NASs) launched between 2009 and 2014 in Canada and the PMPRB7. As shown in Figure 1, Australia, Japan, Netherlands and Korea all launched fewer new active substances (NASs) in Q4 2015 than the OECD median. This level of access represents two-thirds of the access level seen in Canada during the same period. This difference in access suggests that these countries may not be appropriate comparators for Canada; choosing to adopt prices that are similar to those markets may result in similarly reduced access in Canada.

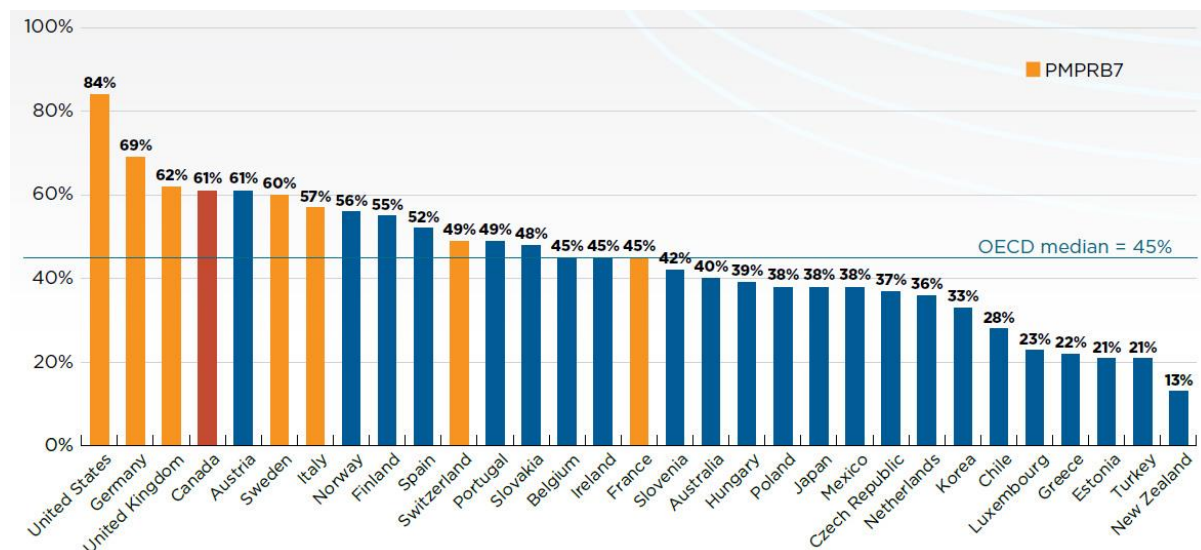


Figure 1: Share of NASs launched by OECD country, Q4-2015³

As shown in Figure 2, particular attention should be given to the inclusion of South Korea in the basket of countries. With only 44% of sales coming from NASs, access to these new medicines in South Korea is well below the OECD median. The inclusion of South Korea could have unforeseen consequences on the Canadian market that could compromise the Minister's commitment to improving access in Canada.

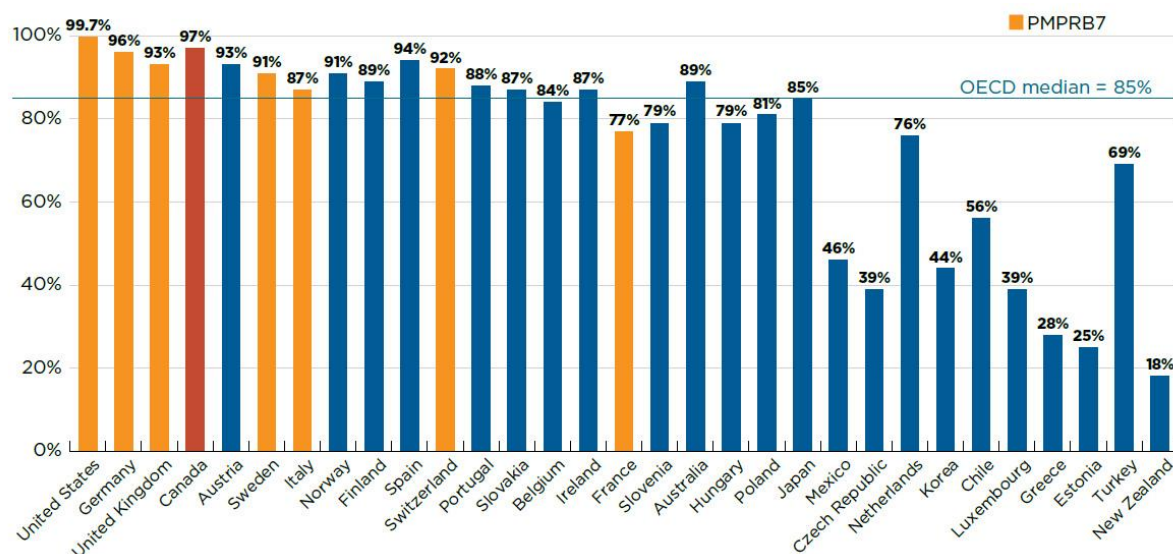


Figure 2: Share of NAS sales by OECD country, Q4-2015

Logistical considerations

Although Roche supports the continued use of international reference pricing (IRP), we believe that IRP should only be used when assessing launch prices. Ongoing use of fluctuating exchange rates when assessing excessive pricing has historically resulted in increased regulatory burden. This is because the prices of medicines tend to become non-compliant when the Canadian dollar strengthens relative to other markets. The current use of exchange rates and price ceilings is further complicated by the fact that industry is not permitted to restore its prices to previous levels once the Canadian dollar returns to its original level. Reliance on IRP exclusively at launch would create a more equitable system for all parties.

Data source considerations

Currently, when assessing pricing data from the PMPRB7 countries, Board Staff uses or derives ex-factory prices from a number of preselected sources. These sources are listed on the PMPRB website.²⁷ Based on existing guidance from the PMPRB regarding the selection of price data sources:

In the event that an ex-factory price is not available in the PMPRB list of recognized sources, the PMPRB will use a consistent approach in determining whether an alternate price source is acceptable. The alternate price source must be both publicly available and publishes an ex-factory price or a retail price when the distribution margins are regulated by a national regulatory body.

The PMPRB decision tree used to determine whether or not a price source should be deemed acceptable for use in international price comparisons is also presented on the PMPRB’s website and has been provided below.

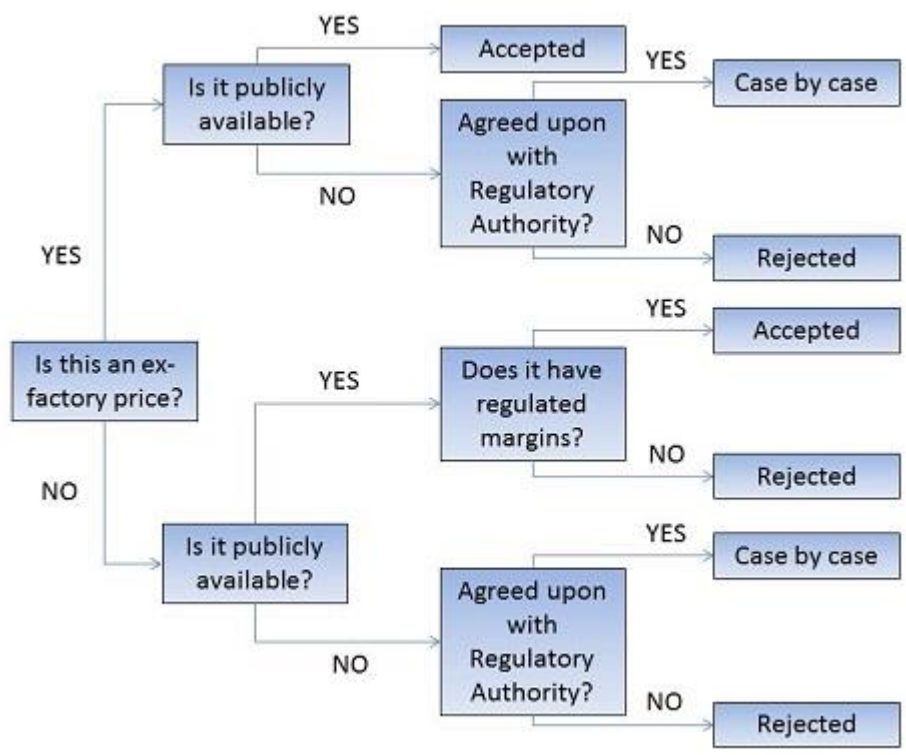


Figure 3: Decision Tree for Determining Foreign Price Sources

There are countries in the PMPRB’s suggested list of 12 countries that do not publish ex-factory prices. Instead, these countries publish Health Insurance Prices or Retail Prices, which include trade margins and value added tax. As noted in Figure 3, those prices sources that do not have regulated margins should be rejected. It is important for Health Canada to determine whether relevant pricing information is available prior to adding it to the Schedule of comparator countries.

Appendix C: Impact of the reporting of discounts and rebates to third party payers

The proposal to require disclosure of third party discounts and rebates is associated with a high level of uncertainty regarding the long-term benefits of this disclosure relative to the increased regulatory burden imposed on manufacturers and the PMPRB. Based on the complexity of some product listing agreements (PLAs) and the manner in which these indirect discounts and rebates are paid, it would appear that the PMPRB will not have the tools it needs to establish fair price ceilings in a timely manner.

Using PLAs to impose price ceilings compromises manufacturers' ability to address payer needs

The Minister's objective of establishing price ceilings based on indirect discounts and rebates is incompatible with the current practice of designing PLAs to address specific payer needs. The design of PLAs ranges from the simple (*i.e.*, percent discount per unit sold) to the complex (*e.g.*, performance-linked reimbursement); however, use of PLAs to establish new price ceilings is only compatible with the use of simple PLAs. This is because use of indirect discounts and rebates to establish price ceilings does not allow for pricing fluctuations. Some examples of how the use of PLAs to set new price ceilings disrupts the current practice of negotiating PLAs to suit the needs of payers are the following:

- The percentage discount provided through PLAs that use volume-based discounts will not be able to decrease with declining utilization of a medicine; it will only be able to increase with increased utilization.
- PLAs that involve annual expenditure caps in an effort to provide payers with budget certainty will no longer be attractive to manufacturers, as the rebate paid in a year where an expenditure cap is exceeded will define the rebate in all future years.
- As drug utilization and treatment effectiveness estimates are prone to higher uncertainty within the populations of smaller drug plans, it is possible that small regional variations (*e.g.*, a change from 1 patient to 2 patients) will result in a sizable impact on price ceilings. This will discourage manufacturers from exploring any complex PLAs.

In short, use of indirect rebate and discount information to establish price ceilings compromises the payer's ability to negotiate agreements that address specific payer needs that are unrelated to price. Given this risk, the reporting of indirect rebates and discounts to the PMPRB in an effort to establish new price ceilings should not be mandated.

Data from invoices may not be available in a timely manner

The logistics of how indirect rebate information will be used by the PMPRB needs to be assessed before its reporting is mandated. The key challenge for the PMPRB will be that not all rebate information is received shortly after the medicine in question has been purchased and used. As part of PLA negotiations, drug plans (both public and private) work with manufacturers to determine the frequency with which invoices will be issued and rebates will be paid. The frequency of invoicing may depend on one of several factors:

PLA design: The complexity of the agreement negotiated between the manufacturer and the payer can influence the frequency of invoicing, with simple percentage discount-based PLAs being appropriate for

quarterly invoicing and more complicated agreements such as annual utilization caps requiring a full year of data prior to calculating the appropriate rebate amount and issuing an invoice.

Payer preference: For administrative reasons, payers may desire to submit invoices to manufacturers quarterly, semi-annually, or annually.

As invoice data may not be available until more than a year after a medicine has been purchased and used, the PMPRB's ability to use these data to establish price ceilings will be compromised. Efforts to compensate for this issue may result in increased regulatory burden, as has been seen with the current practice of reporting direct discounts and rebates.