

Working Group to Inform the Patented
Medicine Prices Review Board (PMPRB)
Steering Committee on Modernization of
Price Review Process Guidelines

Final Report

March 2019

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Purpose

The purpose of this report is to summarise the deliberations and recommendations of the Working Group to Inform the Patented Medicine Prices Review Board (PMPRB) Steering Committee on Modernization of Price Review Process Guidelines.

Introduction

In June 2018, the PMPRB established a *Steering Committee on Modernization of Price Review Process Guidelines* (hereafter the 'Steering Committee'). Its mandate was to assist the PMPRB in synthesizing stakeholder views on key technical and operational modalities of the PMPRB's new draft Guidelines.

In July 2018, the PMPRB established the *Working Group to Inform the Patented Medicine Prices Review Board (PMPRB) Steering Committee on Modernization of Price Review Process Guidelines* (hereafter the 'Working Group'). Its mandate was to inform the Steering Committee on certain issues that the Steering Committee believed would benefit from the review of experts in health technology assessment and other economic and scientific matters.

This report provides a summary of the Working Group's deliberations and recommendations.

Membership

The chair of the Working Group was Dr Mike Paulden (University of Alberta).

Twelve individuals sat as members of the Working Group (listed alphabetically):

1. Sylvie Bouchard (INESSS)¹ [represented by Patrick Dufort and Marie-Claude Aubin];
2. Dr Chris Cameron (Dalhousie University and Cornerstone Research Group);
3. Dr Doug Coyle (University of Ottawa);
4. Don Husereau (University of Ottawa);
5. Dr Peter Jamieson (University of Calgary);
6. Dr Frédéric Lavoie (Pfizer Canada) (*Industry Representative*);
7. Karen Lee (University of Ottawa and CADTH)²;
8. Dr Christopher McCabe (University of Alberta and Institute of Health Economics);
9. Dr Stuart Peacock (Simon Fraser University and BC Cancer Agency);
10. Maureen Smith (*Patient*);
11. Geoff Sprang (Agmen) (*Industry Representative*);
12. Dr Tania Stafinski (University of Alberta).

Two individuals sat as observers of the Working Group:

1. Edward Burrows (Innovation, Science and Economic Development);
2. Nelson Millar (Health Canada).

One individual acted as an external reviewer of the Working Group's draft report:

1. Dr Mark Sculpher (University of York).

An additional individual from CADTH, Dr Tammy Clifford, accepted an invitation to sit as a member of the Working Group but did not participate in the Working Group's deliberations. Dr Clifford also did not contribute towards, or vote on, the Working Group's recommendations.

¹ INESSS: Institut national d'excellence en santé et services sociaux

² CADTH: Canadian Agency for Drugs and Technologies in Health

Terms of Reference

The Terms of Reference (Appendix 4) required that the Working Group examine and make recommendations with respect to specific considerations and questions within the following six 'areas of focus':

1. Options for determining what medicines fall into 'Category 1'

- *A Category 1 medicine is one for which a preliminary review of the available clinical, pharmacoeconomic, market impact, treatment cost and other relevant data would suggest is at elevated risk of excessive pricing.*
- *The following criteria have been identified as supporting a Category 1 classification:*
 - A. *The medicine is 'first in class' or a 'substantial' improvement over existing options*
 - B. *The medicine's opportunity cost exceeds its expected health gain*
 - C. *The medicine is expected to have a high market impact*
 - D. *The medicine has a high average annual treatment cost*
- *Should other criteria be considered? What are the relevant metrics for selecting medicines that meet the identified criteria and what options exist for using these metrics?*

2. Application of supply-side cost effectiveness thresholds in setting ceiling prices for Category 1 medicines

- *Potential approaches for implementing a price ceiling based on a medicine's opportunity cost.*
- *Potential approaches for allowing price ceilings above opportunity cost for certain types of medicines (e.g. pediatric, rare, oncology, etc)*

3. Medicines with multiple indications

- *Options for addressing medicines with multiple indications (e.g. multiple price ceilings or a single ceiling reflecting one particular indication).*

4. Accounting for uncertainty

- *Options for using the CADTH and/or INESSS reference case analyses to set a ceiling price.*
- *Options for accounting for and/or addressing uncertainty in the point estimate for each value-based price ceiling.*

5. **Perspectives**

- *Options to account for the consideration of a public health care system vs societal perspective, including the option of applying a higher value-based price ceiling in cases where there is a ‘significant’ difference between price ceilings under each perspective.*
- *How to define a ‘significant’ difference in price ceilings between each perspective.*

6. **Application of the market size factor in setting ceiling prices**

- *Approaches to derive an appropriate affordability adjustment to a medicine’s ceiling price based on an application of the market size and GDP factors (e.g. based on the US ‘ICER’ [Institute for Clinical and Economic Review] approach).*

Under the Terms of Reference, the Steering Committee had the opportunity to specify additional areas of focus for the Working Group. The Steering Committee did not identify any additional areas of focus for the Working Group to consider.

Objections

The industry members (Frédéric Lavoie and Geoff Sprang) repeatedly raised objections to what they regarded as the “*very narrow boundaries*” established by the Terms of Reference.

Among these objections was a concern that the Working Group was not permitted to examine whether the PMPRB *should* be considering economic factors as part of the proposed reforms, nor any logistical or operational issues associated with implementation of the proposed reforms.

The industry members also stated that, as representatives of BIOTECanada and Innovative Medicines Canada (IMC), they “*do not support the inclusion of proposed economic factors in a quasi-judicial price ceiling regulatory methodology given the uncertainty these factors would introduce, their practical challenges and complexity of implementation*”, arguing that “*the government’s regulatory objectives can be achieved by much simpler, more transparent and predictable mechanisms that will ensure access to necessary prescription medications while achieving the regulatory “bright lines” which PMPRB has recognized as a key consideration*”.

The industry members submitted a number of ‘on the record’ comments to the chair regarding these and other matters, all of which are reproduced *verbatim* in Appendix 3.1 to 3.5.

The patient member (Maureen Smith) also submitted ‘on the record’ comments regarding these and other matters, which are reproduced *verbatim* in Appendix 3.6.

Policy intent

The PMPRB provided the Working Group with a copy of the *Regulations Amending the Patented Medicines Regulations*, as published in Canada Gazette Part I: Vol 151 (2017). This document includes a *Regulatory Impact Analysis Statement* and the *Proposed Regulatory Text* and is reproduced in Appendix 5.1.

The Working Group was instructed by the PMPRB to make its considerations and recommendations on the assumption that the Regulations Amending the Patented Medicines Regulations will remain unchanged in their final publication.

The Working Group therefore considered the Regulatory Impact Analysis Statement and Proposed Regulatory Text as providing a definitive statement of the policy intent with respect to the proposed regulations.

In addition, the PMPRB provided three supporting documents to aid the Working Group in understanding the policy intent:

1. PMPRB Guidelines Scoping Paper (Appendix 5.2);
2. PMPRB Framework Modernization Presentation (Appendix 5.3);
3. PMPRB Short Primer (Appendix 5.4).

The chair sought clarity from the PMPRB in cases where the Working Group was not clear about any aspect of the policy intent.

Process and procedure

The Working Group was convened in July 2018 and met three times in-person and multiple times via teleconference between July 2018 and February 2019:

1. 26 July 2018 (all day in-person meeting);
2. 22 and 24 August 2018 (1 hour teleconference for each of six areas of focus);
3. 24 August 2018 (2 hour teleconference);
4. 25 September 2018 (2 hour teleconference);
5. 12 October 2018 (all day in-person meeting);
6. 28 November 2018 (2 hour teleconference);
7. 5 February 2019 (all day in-person meeting).

The Working Group was originally intended to report in October 2018, but this timeline was extended until March 2019.

Detailed meeting notes were taken by PMPRB staff and emailed to the chair following each meeting. A draft summary of these notes was circulated among Working Group members. In order to encourage a frank and open discussion, the chair committed to not identifying members alongside their comments in the Working Group's report, unless requested to by the member. Members were permitted to provide 'on the record' comments regarding any matters of concern.

One week prior to the final in-person meeting on 5 February 2019, the chair circulated a draft 'Conceptual Framework' to all members. A revised version is reproduced in Appendix 1. The purpose of this 'Conceptual Framework' was to guide members in making consistent recommendations across all six areas of focus, while respecting the policy intent and the range of views expressed by members throughout the Working Group's deliberations.

On 7 February 2019, the chair circulated a set of 'draft potential recommendations'. Members were invited to submit comments or suggested modifications until 15 February 2019.

On 18 February 2019, the chair circulated a draft report of the Working Group's deliberations to all members and the external reviewer, including a final set of 'potential recommendations'.

Under the Terms of Reference, recommendations were determined by a vote of the members, with the chair having the casting vote in the event of a tie. Members were asked to vote on the potential recommendations using an online form, and the full results of the vote were shared with all members. The chair committed not to identify members who voted 'in favour' or 'against' each potential recommendation in the Working Group's final report.

Comments on the draft report, and votes on the potential recommendations, were accepted until 1 March 2019. The final report was submitted to the PMPRB on 6 March 2019.

1: Criteria for classifying medicines as 'Category 1'

1.1 Terms of Reference

Within this area of focus, the Terms of Reference required the Working Group to examine and make recommendations with respect to the following considerations and questions:

A Category 1 medicine is one for which a preliminary review of the available clinical, pharmacoeconomic, market impact, treatment cost and other relevant data would suggest is at elevated risk of excessive pricing.

The following criteria have been identified as supporting a Category 1 classification:

- A. The medicine is 'first in class' or a 'substantial' improvement over existing options;*
- B. The medicine's opportunity cost exceeds its expected health gain;*
- C. The medicine is expected to have a high market impact;*
- D. The medicine has a high average annual treatment cost.*

Should other criteria be considered? What are the relevant metrics for selecting medicines that meet the identified criteria and what options exist for using these metrics?

The chair clarified with the PMPRB whether the Terms of Reference permitted the Working Group to consider whether any of the criteria should be *omitted*. The PMPRB confirmed that such a consideration was within the purview of the Working Group.

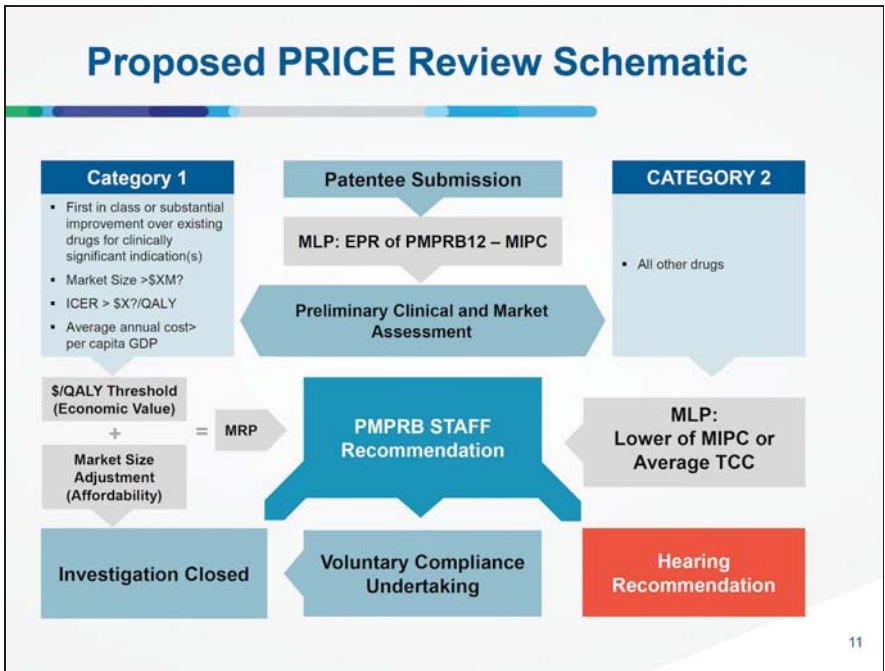
1.2 Policy Intent

The PMPRB Guidelines Scoping Paper includes the following statement which provides context regarding the policy intent with respect to this area of focus:

*“The second part of the framework consists of a screening phase which would **classify new patented drugs as either high or low priority** based on their anticipated impact on Canadian consumers, including individual patients and institutional payers (e.g., public and private drug plans). At this stage in the process, the PMPRB would consider whether the drug is **first in class**, has **few or no therapeutic alternatives**, provides **significant therapeutic improvement over existing treatment options**, is **indicated for a condition that has a high prevalence in Canada**, is a **high cost drug** (i.e. an average annual cost higher than a GDP-based threshold) or is **classified as a high priority drug by other agencies/regulators in the health care system** (such as the Canadian Agency for Drugs and Technologies in Health (CADTH) or Health Canada) because of **unmet medical need**. Drugs that appear to be **high priority** based on these screening factors would be subject to **automatic investigation and a comprehensive review** to determine whether their price is potentially excessive.”*

*(p.6, **emphasis added**)*

The PMPRB Framework Modernization Presentation includes the following slide which provides context regarding the policy intent with respect to this area of focus:



1.3 Summary of Deliberations

There was widespread agreement among members of the Working Group that not all medicines require the same extent of review, and that a ‘risk-based’ approach is desirable.

However, there was debate among the Working Group regarding the criteria that should be used by the PMPRB to identify medicines at elevated risk of excessive pricing (‘Category 1’).

1.3.1 No other criteria considered

Under the Terms of Reference, the Working Group was required to examine and make recommendations regarding whether “other criteria” should be considered by the PMPRB.

No members of the Working Group proposed that any other criteria be considered beyond those specified in the Terms of Reference.

The following *potential* recommendation was put to a vote of the Working Group:

1.1: The Working Group does not recommend any additional criteria beyond those specified in the Terms of Reference.

Members voted **12 in favour** and **0 against** this potential recommendation.

This was therefore **adopted** as a formal recommendation of the Working Group.

1.3.2 ‘Substantial improvement over existing options’

A number of members expressed concern about the wording of Criterion A (*‘The medicine is first in class’ or a ‘substantial’ improvement over existing options*).

Although there was general agreement that ‘first in class’ medicines should be classified as ‘Category 1’, many members questioned why medicines that offer “a ‘substantial’ improvement over existing options” should be classified as ‘Category 1’ if none of the other criteria are met.

Concern was raised by some members that inclusion of this term might penalize manufacturers for producing medicines that offer ‘substantial improvement’, disincentivizing their development. Some members questioned whether this would, in turn, undermine the policy intent.

The chair asked the PMPRB to clarify the policy intent behind the inclusion of this term. The PMPRB responded that medicines that offer a 'substantial' improvement over existing options are more likely to dominate their respective market, increasing the risk of 'excessive pricing'.

Some members argued that, even if a medicine dominates its market, if the medicine does not have 'high' market impact or a 'high' average annual treatment cost then the number of patients affected will be relatively small. Within a 'risk based' approach to classifying medicines, this might justify excluding the 'substantial improvement' term from Criteria A. One member dissented from this position, arguing that the PMPRB has a mandate to protect consumers from 'excessive prices', even if the number of patients affected is small.

Members of the Working Group were unable to identify examples of medicines which offer a 'substantial' improvement over existing options but would *not* be considered 'first in class' and would *not* have 'high' market impact or a 'high' average annual treatment cost. Even if inclusion of the 'substantial improvement' term is consistent with the policy objective, this raises the question as to whether its inclusion is redundant, given the presence of these other criteria.

The following *potential* recommendation was put to a vote of the Working Group:

1.2: The Working Group recommends that the PMPRB consider whether the wording "substantial improvement over existing options" within Criterion A is redundant or inconsistent with the policy intent, and, if so, remove this from consideration.

Members voted **11 in favour** and **1 against** this potential recommendation.

This was therefore **adopted** as a formal recommendation of the Working Group.

1.3.3 'Opportunity cost' criterion

There was widespread agreement that Criterion B (*'The medicine's opportunity cost exceeds its expected health gain'*) should not be considered when classifying medicines as 'Category 1'.

Some members cited the logistical difficulty of establishing cost-utility estimates for all newly launched medicines, rather than only those classified as Category 1. However, since logistical issues were not within scope of the Terms of Reference, these issues were not considered by the Working Group.

The industry members argued that the PMPRB's proposed \$30,000 per quality-adjusted life year (QALY) threshold is sufficiently low as to capture over 90% of all new medicines, such that classification as 'Category 1' would not serve as a useful screening mechanism. A potential response to this specific concern would be to raise the threshold used for screening to a sufficiently high level that a manageable number of new medicines are classified 'Category 1'.

Another reason for excluding Criterion B, given by some members and consistent with the Conceptual Framework, is that this criterion may be redundant in the presence of the other criteria. If a medicine does not satisfy *any* of the other criteria - that is, it does not have a 'high' average annual cost, does not have 'high' market impact, is not 'first in class' and does not offer a 'substantial improvement' over existing treatment - then the potential loss in consumer surplus that might result from its adoption is limited, regardless of the incremental cost-effectiveness ratio (ICER). Under a risk-based approach, it may therefore be better to focus the resources available for assessing 'Category 1' medicines on medicines with 'high' average annual treatment cost, 'high' market impact and/or the potential to dominate their respective market.

The following *potential* recommendation was put to a vote of the Working Group:

1.3: The Working Group recommends that Criterion B be removed from consideration.

Members voted **11 in favour** and **1 against** this potential recommendation.

This was therefore **adopted** as a formal recommendation of the Working Group.

1.3.4 'High average annual treatment cost'

There was disagreement amongst the Working Group regarding Criterion D ('*The medicine has a high average annual treatment cost*'), specifically whether 'high average annual treatment cost' should be considered in absolute terms or as *incremental* upon existing treatment.

It was noted that a new medicine could have 'high average annual treatment cost', but might replace an existing treatment that *also* has 'high average annual treatment cost', such that the *incremental* average annual treatment cost is not 'high'.

Some members noted that, if the *existing* treatment has 'high average annual treatment cost', this increases the risk that the existing treatment is itself considered to be 'excessively priced'. In such cases, the new medicine may also be considered to be 'excessively priced', even if the *incremental* average annual treatment cost is not 'high'.

As noted in the Conceptual Framework, the opportunity cost of adopting a new medicine is a function of its *incremental* cost compared to existing treatment. All else equal, the risk that adopting a new medicine will result in negative consumer surplus would therefore be expected to be greater for a medicine with high *incremental* average annual treatment cost, compared to a medicine with high *absolute* average annual treatment cost but low *incremental* average annual treatment cost. For this reason, the PMPRB may wish to consider ‘average annual treatment cost’ within Criterion D as being *incremental* upon existing treatment.

There are several considerations that would need to be made when calculating this incremental cost. The relevant treatment comparator would need to be established and the cost of treatment with the comparator estimated over the relevant time horizon. If the comparator is itself a patented medicine, then consideration would also need to be given to any expected reduction in the cost of the comparator should generic alternatives to the comparator become available during the patent life of the new medicine.

The following *potential* recommendation was put to a vote of the Working Group:

1.4: The Working Group recommends that “average annual treatment cost” within Criterion D be considered as incremental upon existing treatment.

Members voted **11 in favour** and **1 against** this potential recommendation.

This was therefore **adopted** as a formal recommendation of the Working Group.

1.3.5 Relevant metrics

The Terms of Reference required that the Working Group examine and make recommendations regarding the “*relevant metrics for selecting medicines that meet the identified criteria*”.

The chair interpreted this as referring to the measures and definitions used for each criteria.

For example, if the term ‘substantial improvement’ is retained in Criterion A, how would ‘improvement’ be measured and how would a ‘substantial improvement’ be defined?

There was general agreement that the most appropriate metrics for each criterion would be those already used in Canadian practice. For example, if the PMPRB retains consideration of the ‘substantial improvement’ term in Criterion A, then the definition of ‘substantial improvement’ could be based upon the definition already adopted by the PMPRB. Other potential sources for definitions suggested by members included health technology assessment (HTA) and regulatory agencies in Canada.

The following *potential* recommendation was put to a vote of the Working Group:

1.5: The Working Group recommends that the measures and definitions used for each criterion reflect existing Canadian practice.

Members voted **10 in favour** and **2 against** this potential recommendation.

This was therefore **adopted** as a formal recommendation of the Working Group.

1.3.6 Determining a threshold for each criterion

In addition to identifying “relevant metrics”, the Terms of Reference required that the Working Group examine and make recommendations regarding “options” for using these metrics.

There was some discussion regarding how to determine an appropriate ‘threshold’ to adopt for each criterion, building upon some potential thresholds proposed by the PMPRB.

At the first meeting of the Working Group, the PMPRB proposed that, in considering Criterion B (*‘The medicine’s opportunity cost exceeds its expected health gain’*), the ICER could potentially be compared to a threshold of \$30,000 per quality-adjusted life year (QALY). This was based on an estimate by Ochalek *et al.* (2018) of the opportunity cost of funding new medicines within Canada’s public health care systems (considered further in Topic 2).¹ Some members raised concern that a \$30,000 per QALY threshold would be sufficiently low as to capture a substantial proportion of all new medicines considered by the PMPRB, such that categorization as ‘Category 1’ might not serve as a useful ‘screening’ mechanism. However, in light of the general consensus among the Working Group that Criterion B should not be considered by the PMPRB, no further discussion of this threshold took place.

The PMPRB also proposed a potential ‘market impact’ threshold of either \$20m or \$40m, and proposed that a medicine could be considered to be of ‘high market impact’ if it reached this threshold in any one of either the first 3 years or 5 years after launch. The PMPRB provided the Working Group with estimates of the proportion of all medicines that would be classified as ‘Category 1’ under each combination of these potential thresholds (based solely on Criterion C):

- \$20m market size in any one of the first 3 years: 22% of all medicines
- \$20m market size in any one of the first 5 years: 27% of all medicines
- \$40m market size in any one of the first 3 years: 17% of all medicines
- \$40m market size in any one of the first 5 years: 20% of all medicines

Finally, the PMPRB proposed a potential 'average annual treatment cost' threshold of \$50,000. The PMPRB estimated that this threshold would result in 4% of all medicines being classified as 'Category 1' (based solely on Criterion D).

The Working Group noted that the sensitivity of each criterion as a 'screen' is dependent upon the threshold adopted. The Working Group did not have the necessary data to calculate how many medicines would be classified as 'Category 1' under different combinations of thresholds across the criteria. Furthermore, it was noted that the 'ideal' number of medicines to classify as 'high risk' depends upon the PMPRB's capacity for assessing 'Category 1' medicines (which was unknown to the Working Group), while the 'ideal' types of medicines to classify as 'high risk' depend upon the policy intent.

The Working Group was therefore not in a position to make specific recommendations regarding the threshold to adopt for each criterion. Instead, the chair proposed that the PMPRB should determine the threshold for each criterion, taking into account its capacity for assessing 'Category 1' medicines, the technical considerations of the Working Group, and the policy intent.

The following *potential* recommendation was put to a vote of the Working Group:

1.6: The Working Group recommends that a threshold for each criterion be determined by the PMPRB, taking into account its capacity for assessing 'Category 1' medicines, the technical considerations of the Working Group, and the policy intent.

Members voted **10 in favour** and **2 against** this potential recommendation.

This was therefore **adopted** as a formal recommendation of the Working Group.

1.3.7 Clear specification of the threshold for each criterion

The two industry members on the Working Group emphasized the importance of the PMPRB clearly specifying the threshold to be used for each criterion, so as to provide a “clear bright line” to manufacturers.

A technical justification for this request is that a clear specification of the threshold for each criterion reduces uncertainty. The Conceptual Framework outlines how uncertainty in a medicine’s pharmacoeconomic value may result in an expected loss in economic surplus, such that there may be value in reducing this uncertainty. Similarly, uncertainty in whether a medicine may be subject to ‘Category 1’ classification may impose an expected loss on manufacturers and other stakeholders.

The following *potential* recommendation was put to a vote of the Working Group:

1.7: The Working Group recommends that the threshold for each criterion be clearly specified, so as to reduce uncertainty for stakeholders.

Members voted **12 in favour** and **0 against** this potential recommendation.

This was therefore **adopted** as a formal recommendation of the Working Group.

1.3.8 Other considerations

There was some discussion as to whether ‘high market impact’ should be considered as *incremental* upon existing treatment (similar to the consideration of ‘high average annual treatment cost’ in section 1.3.4). Some members argued that a medicine with high market size may replace an existing treatment which also has high market size, such that the *net* market impact is relatively small.

However, it was apparent from the PMPRB Guidelines Scoping Paper, as well as the proposed ‘market size adjustment’ (section 6), that there is a policy concern regarding medicines with high *absolute* market impact. The PMPRB confirmed to the chair that this was the case. Given this policy intent, the Working Group did not consider any potential recommendation to modify the wording of the ‘high market impact’ criterion so that it is incremental upon existing treatment.

2: Supply-side cost effectiveness thresholds

2.1 Terms of Reference

Within this area of focus, the Terms of Reference required the Working Group to examine and make recommendations with respect to the following considerations and questions:

Potential approaches for implementing a price ceiling based on a medicine's opportunity cost.

Potential approaches for allowing price ceilings above opportunity cost for certain types of medicines (e.g. pediatric, rare, oncology, etc).

2.2 Policy Intent

The Regulatory Impact Analysis Statement includes the following statements which provide context regarding the policy intent with respect to this area of focus:

*“Information regarding pharmacoeconomic value: patentees would be required to provide the PMPRB with all published **cost-utility analyses** that express the value in terms of the **cost per quality-adjusted life year (QALY)**. Cost-utility analyses are viewed by experts as the **“gold standard”** approach to considering the **economic value** of new medicines.”*
*(p.10, **emphasis added**)*

*“Without the proposed amendments, it is estimated that **public health care systems from across Canada** will spend an additional \$3.9 billion (PV) for the same quantity of patented medicine. This represents a significant **opportunity cost for the Canadian public health care system**, as these funds could have been used in **other areas of the health care system to better the health of Canadians.**”*
*(p.16, **emphasis added**)*

The PMPRB Guidelines Scoping Paper includes the following statement which provides context regarding the policy intent with respect to this area of focus:

*“The first part of the test would **assess the incremental cost per quality-adjusted life year (QALY) of the drug, as determined by CADTH’s health technology assessment process, against an explicit cost effectiveness threshold.** The threshold would be based on the **opportunity cost** associated with **displacing the least cost effective health technology in the Canadian health system**, otherwise understood as the marginal cost of a QALY, as calculated by expert health economists and **revised periodically to reflect changing market conditions.** Drugs that **prolong life or provide significant QALY gains** could be subject to a **more generous threshold**, as Canadian payers have demonstrated a **higher willingness to pay for these types of drugs**”.*

*(p.6, **emphasis added**)*

The PMPRB Framework Modernization Presentation includes the following slide which provides context regarding the policy intent with respect to this area of focus:

Part III: MRP for Category 1 drugs

- Step 1: application of pharmacoeconomic factor
 - Empirical work undertaken by Karl Claxton at the University of York suggests a \$30K/QALY opportunity cost threshold for Canada.
 - Question whether and to what extent that estimate should be taken into account in at the screening phase to determine whether a drug should go in Category 1 or Category 2.
 - Category 1 drugs will then be subject to a baseline maximum value-based price ceiling of \$X/QALY, for reasons of practicality and efficiency.
 - Drugs that meet certain clinical characteristics (e.g., high burden of disease or significant absolute gain in QALY) may be subject to a higher \$/QALY ceiling.

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2.3 Summary of Deliberations

The Working Group's deliberations on this topic were informed by two documents commissioned by the PMPRB prior to establishment of the Working Group:

1. A white paper prepared by the Institute of Health Economics (IHE) titled "*Theoretical models of the cost-effectiveness threshold, value assessment, and health care system sustainability*", hereafter referred to as the 'IHE report'.²
2. A report prepared by Jessica Ochalek and colleagues from the University of York titled "*Assessing health opportunity costs for the Canadian health care systems*", hereafter referred to as 'Ochalek *et al.* (2018)'.¹

2.3.1 Appropriateness of using a supply-side threshold

As noted in the IHE report, a supply-side threshold can be used to estimate the 'health opportunity cost' associated with adopting a new medicine within a public health care system. This health opportunity cost is measured in units of health benefit (typically QALYs) and reflects the estimated health 'forgone' by other patients within the health care system if limited resources are used to adopt the new medicine.

For example, Ochalek *et al.* (2018) estimated a supply-side threshold of \$30,000 per QALY for Canada as a whole, with some variation across provinces and territories (considered further in section 2.3.4). This estimate implies that every additional \$30,000 spent on a new medicine results in one forgone QALY by other patients across Canada's public health care systems. A higher estimate of the supply-side threshold would imply that fewer QALYs are displaced at any given incremental cost associated with a new medicine, and conversely a lower supply-side threshold would imply that more QALYs are displaced for any given incremental cost.

Additional explanation and examples are provided in the Conceptual Framework.

There was debate amongst Working Group members as to whether a supply-side threshold is always the most appropriate means for estimating the opportunity cost of new medicines. Specifically, consideration was given as to whether a 'demand-side threshold' might be more appropriate than a supply-side threshold in some cases.

As noted in the IHE report, a demand-side threshold reflects Canadians' 'willingness-to-pay' for health benefits. Some members argued that a demand-side threshold might therefore be a more appropriate threshold for private insurers and patients who pay out-of-pocket.

Nevertheless, in light of the PMPRB’s clarification that the policy intent is to adopt the perspective of the Canadian public health care system (section 5.2), the focus of the Working Group’s deliberations was on a supply-side approach to estimating the threshold.

Since the policy intent is to adopt the perspective of Canada’s public health care systems, and since the Regulatory Impact Analysis Statement views the QALY, as used in cost-utility analysis, as the “gold standard” approach to considering the economic value of new medicines, it follows that the most relevant measure of the opportunity cost of a new medicine, given this policy intent, is an estimate of the QALYs forgone by patients within Canada’s public health care systems. As noted in the Conceptual Framework, this may be estimated using an estimate of the incremental cost of the new medicine and an estimate of a supply-side cost-effective threshold, expressed in terms of cost per QALY.

The following *potential* recommendation was put to a vote of the Working Group:

2.1: The Working Group regards the use of a supply-side cost-effectiveness threshold, as a means for estimating the opportunity cost of adopting new medicines within Canada’s public health care systems, as consistent with the policy intent.

Members voted **10 in favour** and **2 against** this potential recommendation.

This was therefore **adopted** as a formal recommendation of the Working Group.

2.3.2 Uncertainty in the empirical evidence base

The Working Group was unanimous in considering the empirical evidence base with respect to Canadian estimates of supply-side thresholds to be uncertain.

The only existing estimate of a supply-side threshold for Canada is that provided by Ochalek *et al.* (2018). This work reported estimates of supply-side thresholds for each province and territory in terms of cost per disability adjusted life year (DALY) averted. Based on these estimates, the authors argued that “a cost per DALY threshold is likely to be less than \$50,000 for Canada as a whole”. The authors further argued that “a cost per QALY threshold is likely to be similar or lower than a cost per DALY averted threshold”, concluding that “a cost per QALY threshold of \$30,000 per QALY would be a reasonable assessment of the health effects of changes in health expenditure for Canada as a whole and is likely to be similar across most provinces”.

The authors acknowledged that this research was not primarily based upon Canadian data, noting that “*further research to provide Canadian and/or province specific elasticity estimates using within country and within province data should be regarded as a priority*”.

Some members of the Working Group expressed concerns with the instrumental variables (IVs) used by Ochalek *et al.* (2018).

One member noted that the authors employed two specific IVs that are potentially problematic:

1. Military expenditure per capita of neighbouring countries;
2. A measure of institutional quality, captured using:
 - a. The level of infrastructure (proxied by ‘paved roads per square km’);
 - b. Shock in ‘donor funding’ (absolute deviation from the historical mean).

This member viewed the appropriateness of these IVs as questionable in the Canadian context. Canada’s neighbor is the United States, which is an outlier in terms of military expenditure per capita in the sample of countries used in the Ochalek *et al.* (2018) study. Canada is also an outlier in terms of ‘paved roads per square km’, ranking 90th out of 125 countries.³ Since relatively few high income countries receive ‘donor funding’, this member noted that ‘paved roads per square km’ is effectively the sole IV for infrastructure quality.

These potentially ‘weak’ IVs raise concerns about the parameter estimates from the authors’ regression model. Specifically, if the IVs are only weakly correlated with the endogenous regressors, parameter estimates may be biased, estimates may be inconsistent, tests of significance may have incorrect size, and confidence intervals may be wrong.⁴⁻⁶

The following *potential* recommendation was put to a vote of the Working Group:

2.2: The Working Group regards the current evidence base with respect to Canadian estimates of supply-side cost-effectiveness thresholds, including the empirical research by Ochalek *et al.* (2018), as uncertain.

Members voted **12 in favour** and **0 against** this potential recommendation.

This was therefore **adopted** as a formal recommendation of the Working Group.

2.3.3 Direction and magnitude of bias in the \$30,000 per QALY estimate

Given the Working Group's concern with the IVs used in the Ochalek *et al.* (2018) research, members considered the potential direction and magnitude of bias in the \$30,000 per QALY estimate.

At a public seminar, the chair asked the corresponding author of the Ochalek *et al.* (2018) research, Dr Karl Claxton, for his views on the implications of any weakness in the IVs.⁷ Dr Claxton's response was that any weakness in the IVs would be expected to weaken the relationship between health expenditures and health outcomes, in turn resulting in an overestimate of the cost-effectiveness threshold.

The implication of Dr Claxton's remarks is that a re-estimate of the supply-side threshold with stronger IVs would be expected to be below \$30,000 per QALY. However, the Working Group member who initially questioned the strength of the IVs in the Ochalek *et al.* (2018) research disagreed, arguing that the direction of bias as a result of weak IVs is unknown.

The following *potential* recommendation was put to a vote of the Working Group:

2.3: The Working Group regards the direction and magnitude of any bias in the \$30,000 per QALY estimate by Ochalek *et al.* (2018) to be unknown.

Members voted **12 in favour** and **0 against** this potential recommendation.

This was therefore **adopted** as a formal recommendation of the Working Group.

2.3.4 Differences across provinces and territories

Several members noted that a different supply-side threshold would be expected for each Canadian public health care system.

Theoretically, the supply-side threshold is affected by the budget of the health care system in question, among other considerations.⁸ Since each provincial and territorial health care system has its own budget, a different supply-side threshold would be expected for each.

This is consistent with the results of the work by Ochalek *et al.* (2018), which found a different supply-side threshold (in terms of cost per DALY averted) in each province and territory.¹

The Working Group considered several potential approaches for setting a single ceiling price across all provinces and territories, including:

1. A ceiling price at which the medicine is 'just' cost-effective in the province or territory with the highest supply-side threshold;
2. A ceiling price at which the medicine is 'just' cost-effective in the province or territory with the lowest supply-side threshold;
3. A ceiling price at which the medicine is 'just' cost-effective across Canada as a whole.

A consideration of the implications of each approach is provided in the Conceptual Framework. In summary, each approach results in a different allocation of the total 'economic surplus' among 'consumers' (patients) and 'producers' (manufacturers). The first approach results in negative overall consumer surplus, the second approach results in positive overall consumer surplus, while the third approach results in zero overall consumer surplus.

Since the preferred allocation of the economic surplus is a matter for policy makers, the Working Group does not advocate for any specific approach. Instead, the Working Group recommends that any single threshold used for the purpose of informing a ceiling price be consistent with the policy intent, given the technical considerations outlined by the Working Group.

The following *potential* recommendation was put to a vote of the Working Group:

2.4: The Working Group recognizes that each provincial and territorial public health care system has a unique supply-side cost-effectiveness threshold, and recommends that any single threshold used for the purpose of informing a ceiling price be consistent with the policy intent.

Members voted **12 in favour** and **0 against** this potential recommendation.

This was therefore **adopted** as a formal recommendation of the Working Group.

2.3.5 Medicines with large net budget impact

In theory, adopting medicines with a large net budget impact into a budget constrained public health care system would be expected to result in a disproportionately large opportunity cost.^{8,9} (Note that “net budget impact” is distinct from the “market size” consideration in section 6.)

One approach for dealing with this is to use a progressively lower supply-side threshold for medicines with progressively larger net budget impact. One member cited the empirical work by James Lomas, which estimated how the supply-side threshold for the English NHS would fall as the net budget impact of a new health technology increases.⁹ For new hepatitis C treatments, which had an estimated net budget impact of £772m in the first year of use, Lomas found that the supply-side threshold would need to be adjusted down from £12,936 per QALY (the supply-side threshold for marginal changes in health care expenditure) to £12,452 per QALY.^{9,10}

The Working Group was unaware of any other attempts internationally to estimate supply-side thresholds associated with non-marginal changes in health expenditures. Since no equivalent empirical estimates are available for Canada, there is no data to inform such a downwards adjustment to the Canadian supply-side threshold at the present time.

The following *potential* recommendation was put to a vote of the Working Group:

2.5: The Working Group recognizes that, in principle, a downwards adjustment should be applied to the supply-side cost-effectiveness threshold for medicines with substantial net budget impact, but notes that there is no Canadian empirical evidence to inform the magnitude of such an adjustment at the present time.

Members voted **10 in favour** and **2 against** this potential recommendation.

This was therefore **adopted** as a formal recommendation of the Working Group.

2.3.6 Equity weights

The Terms of Reference tasked the Working Group with considering “*Potential approaches for allowing price ceilings above opportunity cost for certain types of medicines (e.g. pediatric, rare, oncology, etc)*”.

The Working Group noted that, under CADTH’s ‘reference case’ requirements, all QALYs are assigned equal value. A justification of this position is provided in CADTH’s ‘Guidelines for the Economic Evaluation of Health Technologies: Canada’ (4th Edition; pp.59-60).¹¹ CADTH’s

reference case therefore reflects an equity position under which a ‘weight’ of 1 is applied to all QALYs, regardless of any characteristics of the patients, disease or technology in question.

Critically, a weight of 1 on all QALYs does not permit a ceiling price “*above opportunity cost*” for “*certain types of medicines*” but not others. The Working Group therefore considered the potential for applying different weights to some QALYs, and hence departing from CADTH’s reference case assumption that all QALYs have equal value.

There is a small but growing empirical literature on the types of characteristics for which society may assign greater or lesser weight when valuing health gains.^{12–18} One member provided the Working Group with a brief summary of this literature. Characteristics that are often found to be important in empirical studies include severity of illness (particularly the presence or otherwise of life threatening or progressively chronically debilitating illness), the availability of active treatment alternatives, the prevalence of disease, the type of health gain (such as a reduction in pain), and the magnitude of health gain. These factors are often found to interact with one another, and so should not be considered independently. In the opinion of this member, greater empirical work is needed to fully understand these interactions and the ‘weights’ that would be put on each characteristic.

Members also discussed theoretical issues associated with applying weights to some QALYs but not others. One member expressed concern that some important conceptual problems have not yet been addressed in the literature - for example, would a greater weight on QALYs for ‘cancer’ apply to all QALYs gained by a patient with cancer (including those gained through treatment for other diseases) or only the QALYs gained through cancer treatment (such that other QALY gains for the same patient for other diseases would be assigned different weight). There is also an ongoing and unresolved debate regarding whether weights should be applied directly to QALYs or to the cost-effectiveness threshold. The latter approach has been used by NICE in the UK but has received criticism for resulting in ‘inconsistencies’ in its consideration of social value.¹⁹

As a result of these limitations in the empirical and theoretical literature, the predominant view of members was that equity weights other than 1 should not be implemented at the present time.

There was some discussion by the Working Group regarding the potential implications of this recommendation for medicines for rare diseases. As noted in the Conceptual Framework, medicines with small market size may be expected to have a higher supply curve (at the respective quantity) than medicines with large market size. Such medicines may therefore be less profitable at a given ceiling price compared to medicines with larger market size. This issue is considered further in section 6.

The following *potential* recommendation was put to a vote of the Working Group:

2.6: The Working Group does not recommend the implementation of 'equity weights' other than 1, as would be required to allow price ceilings above opportunity cost for some medicines but not others, due to limitations in the existing theoretical and empirical evidence base.

Members voted **9 in favour** and **3 against** this potential recommendation.

This was therefore **adopted** as a formal recommendation of the Working Group.

2.3.7 Clear specification of the supply-side threshold

In common with the request that any thresholds used for classifying 'Category 1' medicines be clearly specified (section 1.3.7), the two industry members emphasized the desirability that any supply-side threshold used for the purposes of informing a price ceiling be clearly specified.

As noted in the Conceptual Framework, the supply-side threshold is a key determinant of the location of the 'demand curve' for a new medicine. A technical justification for requesting that the supply-side threshold be clearly specified is that it reduces uncertainty for manufacturers regarding the location of this demand curve, and hence the producer surplus if the ceiling price is informed by this demand curve.

There was general agreement among the Working Group about the desirability of specifying the supply-side threshold, and hence providing greater clarity to manufacturers and other stakeholders regarding the location of the demand curve.

Nevertheless, as noted in the Conceptual Framework, there is also considerable uncertainty about the location of the manufacturer's 'supply curve'. This increases uncertainty regarding the set of possible ceiling prices at which consumer and producer surplus are both positive, potentially resulting in a loss of economic surplus for both consumers and producers. To minimize this uncertainty, efforts should be made to better understand the location of the supply curve for new medicines. This would complement efforts to provide greater certainty regarding the location of the demand curve through a clear specification of the supply-side threshold.

The following *potential* recommendation was put to a vote of the Working Group:

2.7: The Working Group recommends that any estimate of the supply-side threshold adopted by the PMPRB for the purposes of informing a price ceiling be clearly specified, so as to reduce uncertainty for stakeholders.

Members voted **12 in favour** and **0 against** this potential recommendation.

This was therefore **adopted** as a formal recommendation of the Working Group.

2.3.8 Further empirical research

Given the uncertainties in the existing empirical evidence base regarding Canadian supply-side cost-effectiveness thresholds (sections 2.3.2 and 2.3.3), there was broad support among members of the Working Group for conducting further empirical research.

Since differences in supply-side thresholds across provinces and territories are predicted by theoretical work and were observed by Ochalek *et al.* (2018) (section 2.3.4), there was also agreement that any future Canadian empirical studies should consider potential variation in estimates of supply-side cost-effectiveness thresholds across jurisdictions within Canada.

The following *potential* recommendation was put to a vote of the Working Group:

2.8: The Working Group recommends that the PMPRB support further empirical research to estimate a supply-side cost-effectiveness threshold for Canada. This research should consider and report on variation in estimates of supply-side cost-effectiveness thresholds across jurisdictions within Canada.

Members voted **12 in favour** and **0 against** this potential recommendation.

This was therefore **adopted** as a formal recommendation of the Working Group.

2.3.9 Specifying an ‘interim’ threshold

Since the existing empirical evidence on Canadian supply-side thresholds was considered to be uncertain, and since further empirical research will take time to conduct and report, members discussed how a threshold might be specified by the PMPRB in the interim.

Existing Canadian policy thresholds

One potential interim approach considered by the Working Group is for the PMPRB to specify a threshold in line with existing ‘policy thresholds’ used by Canadian HTA agencies.

The Working Group observed that no Canadian HTA agencies currently specify an explicit cost per QALY policy threshold. However, one member noted that INESSS uses an informal policy threshold of \$50,000 to \$100,000 per QALY, with other members providing anecdotal evidence of similar policy thresholds being used informally by other HTA agencies in Canada (with higher policy thresholds used in some cases, such as for cancer).

Another member suggested that it may be useful to understand what policy threshold is informally used by the the pan-Canadian Pharmaceutical Alliance (pCPA) in its negotiations.

One member cited a 2016 article in the Hamilton Spectator, which reported that *“the pan-Canadian Oncology Drug Review has set an unofficial threshold of \$100,000 per quality-adjusted life year for new cancer medications”*, and also a 2009 letter by the Deputy Minister of Health and Long-Term Care for Ontario, which noted that the Committee to Evaluate Drugs *“typically considers a range of \$40-60,000 [per] QALY as an acceptable range”*.^{20,21}

Taken together, this evidence suggests that informal policy thresholds used by HTA agencies in Canada are in the region of \$50,000 to \$100,000 per QALY, with oncology medicines assessed at the higher end of this range and other medicines assessed relatively lower within this range.

It should be noted that none of these policy thresholds is based on an empirical assessment of the opportunity cost of adopting new medicines within Canada’s public health care systems, as would be required to specify a ‘supply-side’ threshold.

Supply-side thresholds from other jurisdictions

Another potential interim approach is to consider empirical estimates of supply-side thresholds for other jurisdictions with similar wealth and medicine market characteristics as Canada.

The IHE report summarized three existing published estimates of supply-side thresholds for other jurisdictions:²

1. The work by Claxton *et al.* (2015), which estimated a supply-side threshold of £12,936 per QALY for the public health care system in the UK.¹⁰
2. The work by Vallejo-Torres *et al.* (2017), which estimated a supply-side threshold of between €21,000 and €25,000 per QALY for the public health care system in Spain.²²
3. The work by Edney *et al.* (2017), which estimated a supply-side threshold of AU\$28,033 per QALY for the public health care system in Australia.²³

The chair noted that the \$30,000 per QALY estimate from Ochalek *et al.* (2018) is broadly in line with these estimates, and that all three of these countries are on the proposed PMPRB12 list of countries with “*reasonably comparable economic wealth*” and “*similar medicine market size characteristics*” as Canada. Absent reasons why Canada would be considered an ‘outlier’ among PMPRB12 countries, one might therefore reasonably expect a future Canadian estimate of a supply-side threshold to be similar to the estimates reported in these countries. Nevertheless, given the various determinants of the supply-side threshold, some variation in estimates across countries would be expected.⁸

The following *potential* recommendation was put to a vote of the Working Group:

2.9: The Working Group recommends that any ‘interim’ threshold specified by the PMPRB prior to completion of further Canadian empirical work should be informed by a comprehensive consideration of existing thresholds used by Canadian HTA agencies and empirical estimates of supply-side thresholds from other relevant jurisdictions.

Members voted **10 in favour** and **2 against** this potential recommendation.

This was therefore **adopted** as a formal recommendation of the Working Group.

3: Multiple indications

3.1 Terms of Reference

Within this area of focus, the Terms of Reference required the Working Group to examine and make recommendations with respect to the following considerations and questions:

Options for addressing medicines with multiple indications (e.g. multiple price ceilings or a single ceiling reflecting one particular indication).

3.2 Policy Intent

The Regulatory Impact Analysis Statement includes the following statements which provide context regarding the policy intent with respect to this area of focus:

*“The **price paid** for a medicine should take into consideration the **value it produces.**”*

*(p.8, **emphasis added**)*

The PMPRB Guidelines Scoping Paper includes the following statement which provides context regarding the policy intent with respect to this area of focus:

*“The fifth and final part of the new framework would involve the **periodic “re-benching” of drugs** to ensure that previous determinations of potential excessive pricing and/or price ceilings remain relevant in light of **new indications** (resulting in a change of market size) or changes in market conditions. Depending on the nature of the change, **the re-benching process could result in a decrease or increase in ceiling price.**”*

*(p.7, **emphasis added**)*

3.3 Summary of Deliberations

Two broad approaches were considered by the Working Group: a separate ceiling price for each indication ('indication-specific pricing'), or a single ceiling price across all indications.

There was general agreement that indication-specific pricing is the more appealing approach in principle. As noted in the Conceptual Framework, the incremental effectiveness of any medicine generally differs across indications. Indication-specific pricing would permit the ceiling price of the medicine to reflect this differing value for each indication. This would appear to closely align with the policy intent, as stated in the Regulatory Impact Analysis Statement, that "*the price paid for a medicine should take into consideration the value it produces*".

However, although one member was of the view that multi-indication pricing may be feasible for some 'Category 1' medicines, several members expressed concern that indication-specific pricing is not possible in Canada, given current limitations in data capture and reporting.

It was noted that indication-specific pricing requires an IT infrastructure for collecting data on volume per indication. An informal review conducted by one member identified a number of different approaches internationally.^{24,25} France, Germany and Australia all use indication-specific pricing, based on expected patient volumes for each indication. Italy engages in risk-sharing arrangements using indication-specific patient registries. Express Scripts in the United States is using indication-specific pricing for cancer medicines, and the UK piloted the feasibility of this approach using the Systemic Anti-Cancer Therapy Dataset (SACT) data set. Belgium and Spain have also used indication-specific pricing for expensive medicines and hospital-based medicines, respectively.

Since logistical and implementation issues were out of the scope of the Terms of Reference, Working Group members did not give detailed consideration to the feasibility of implementing indication-specific pricing in Canada. Instead, the Working Group's deliberations focused exclusively on options for specifying a single ceiling price across multiple indications.

3.3.1 Specifying a single ceiling price across all indications

The Working Group considered several potential approaches for setting a single ceiling price across multiple indications, including:

1. A ceiling price at which the medicine is 'just' cost-effective in the most cost-effective indication;
2. A ceiling price at which the medicine is 'just' cost-effective in the least cost-effective indication;
3. A ceiling price at which the medicine is 'just' cost-effective across all indications;
4. A ceiling price at which the medicine is 'just' cost-effective in the first indication considered by the PMPRB.

A consideration of the implications of each approach is provided in the Conceptual Framework.

In common with the different potential approaches for setting a ceiling price across provinces and territories (section 2.3.4), each approach results in a different allocation of the total economic surplus among consumers and producers. The first approach results in negative overall consumer surplus, the second approach results in positive overall consumer surplus, the third approach results in zero overall consumer surplus, while the fourth approach results in zero expected consumer surplus if manufacturers do not behave strategically when launching medicines or negative expected consumer surplus if manufacturers do behave strategically.

At the final in-person meeting, the PMPRB asked the chair to consider a fifth potential approach for setting a single ceiling price across multiple indications:

5. A ceiling price at which the medicine is 'just' cost-effective in one specific 'key' indication identified by the PMPRB.

This approach has similarities to the fourth approach considered above, insofar as the ceiling price would be based upon the cost-effectiveness of the new medicine in one indication only. It would also share an advantage that the fourth approach has over the first three approaches, insofar as the ceiling price would not need to be rebenchmarked over time as new indications are launched (unless the 'key' indication were to change).

The implications for the allocation of the total economic surplus with this fifth approach depend upon whether the 'key' indication is more or less cost-effective than other indications. If this 'key' indication is the most cost-effective, then the implications are the same as for the first approach, with negative overall consumer surplus. Alternatively, if the 'key' indication is the least cost-effective, then the implications are the same as for the second approach, with positive overall consumer surplus. In both cases consumer surplus in the 'key' indication is zero.

As with the consideration of different potential approaches for setting a ceiling prices across provinces and territories (section 2.3.4), the Working Group does not advocate for any specific approach since the preferred allocation of the economic surplus is a matter for policy makers. Instead, the Working Group recommends that any single threshold used for the purpose of informing a ceiling price be consistent with the policy intent, given the technical considerations outlined by the Working Group.

The following *potential* recommendation was put to a vote of the Working Group:

3.1: The Working Group recommends that the PMPRB specify a single ceiling price for each medicine that applies across all indications and is consistent with the policy intent.

Members voted **12 in favour** and **0 against** this potential recommendation.

This was therefore **adopted** as a formal recommendation of the Working Group.

4: Accounting for uncertainty

4.1 Terms of Reference

Within this area of focus, the Terms of Reference required the Working Group to examine and make recommendations with respect to the following considerations and questions:

Options for using the CADTH and/or INESSS reference case analyses to set a ceiling price.

Options for accounting for and/or addressing uncertainty in the point estimate for each value-based price ceiling.

4.2 Policy Intent

The Regulatory Impact Analysis Statement includes the following statements which provide context regarding the policy intent with respect to this area of focus:

*“In recognition of the significant expertise that can be necessary to prepare and validate cost-utility analyses, **reporting would be limited to those that have been prepared by a publicly funded Canadian organization, such as the Canadian Agency for Drugs and Technologies in Health (CADTH) or the Institut national d’excellence en santé et services sociaux (INESSS)**. These organizations have dedicated expertise, and they generally conduct pharmacoeconomic analyses for medicines seeking to be reimbursed by public insurers. **The PMPRB would consider these analyses in its evaluation of price excessiveness. It would not duplicate the work conducted by CADTH and INESSS as part of reimbursement processes.**”*

(pp.10-11, **emphasis added**)

None of the documents provided to the Working Group by the PMPRB included any statement regarding the policy intent with respect to *“options for accounting for and/or addressing uncertainty in the point estimate for each value-based price ceiling”*.

4.3 Summary of Deliberations

4.3.1 Using the CADTH and/or INESSS reference case analyses

The Terms of Reference tasked the Working Group with considering “*options for using the CADTH and/or INESSS reference case analyses to set a ceiling price*”.

Members discussed how the results of pharmacoeconomic analyses of a medicine reported by CADTH, INESSS and other Canadian HTA agencies generally differ from those reported by the manufacturer and also from each other. The industry members argued that cost-utility estimates by CADTH and INESSS “*often exhibit differences in their estimates pertaining to heterogeneous assumptions and expert opinions*”, and that this variability is “*a function of the analyst that produces the assessment and the peer reviewers that challenge the analyses*”.

Members also discussed whether the assumptions adopted by CADTH and INESSS in their ‘reference case’ analyses are appropriate for use by the PMPRB when setting ceiling prices. Some members suggested that the PMPRB might wish to establish its own ‘reference case’, clearly specifying the requirements and any necessary assumptions for pharmacoeconomic analyses used to inform ceiling prices. Although the policy intent is to “*not duplicate the work conducted by CADTH and INESSS*”, possible departures from existing CADTH and INESSS reference case assumptions include a clear specification of a supply-side cost-effectiveness threshold and a potential departure from the assumption of risk-neutrality (see section 4.3.3).

Since matters of process were beyond the remit given by the Terms of Reference, the Working Group did not consider what specific processes might be established by the PMPRB to arrive at a single set of pharmacoeconomic results from which to inform a ceiling price. Nevertheless, there was a widespread view among Working Group members that clarity is required in whatever processes are established by the PMPRB.

The following *potential* recommendation was put to a vote of the Working Group:

4.1: The Working Group recognizes that there is variation in the results of pharmacoeconomic analyses reported by CADTH and INESSS, and recommends that the PMPRB establish clear processes for identifying how these analyses will be used to inform a ceiling price.

Members voted **12 in favour** and **0 against** this potential recommendation.

This was therefore **adopted** as a formal recommendation of the Working Group.

4.3.1 Ensuring unbiased estimates

The Working Group noted that the most recent edition of CADTH's 'Guidelines for the Economic Evaluation of Health Technologies: Canada' (4th Edition) includes specific recommendations for addressing uncertainty in pharmacoeconomic analysis.¹¹ These include an assessment of parameter uncertainty (through probabilistic analysis), structural uncertainty (through scenario analysis), and methodological uncertainty (through a comparison of 'reference case' and 'non-reference case' analyses). INESSS has similar requirements for considering uncertainty.²⁶

Some members expressed concern that not all pharmacoeconomic analyses currently satisfy these recent CADTH guidelines, and that better enforcement of these guidelines is needed to ensure that uncertainty is appropriately addressed in all pharmacoeconomic analyses considered by the PMPRB when informing ceiling prices.

Members also noted that current HTA processes at CADTH and INESSS are undertaken for the purpose of assisting public payers in making decisions related to funding and informing pricing negotiations, rather than to inform ceiling prices set by the PMPRB. There was broad agreement that the PMPRB should engage with CADTH and INESSS, and any other relevant stakeholders, regarding modifications that may be required to these processes given the proposed change in the context of their use.

While considerations of the specific processes adopted by CADTH and INESSS are beyond the scope of the Working Group, the key *technical* principle is that all pharmacoeconomic analyses should satisfy the same basic set of requirements, including a comprehensive and unbiased assessment of parameter uncertainty, structural uncertainty and methodological uncertainty.

The following *potential* recommendation was put to a vote of the Working Group:

4.2: The Working Group recommends that all pharmacoeconomic analyses used for the purpose of informing a ceiling price should satisfy the requirements of the most recent edition of CADTH's 'Guidelines for the Economic Evaluation of Health Technologies: Canada', including an unbiased assessment of parameter uncertainty, structural uncertainty and methodological uncertainty.

Members voted **12 in favour** and **0 against** this potential recommendation.

This was therefore **adopted** as a formal recommendation of the Working Group.

4.3.2 Addressing uncertainty in the point estimate

The Terms of Reference also required the Working Group to consider “*options for accounting for and/or addressing uncertainty in the point estimate for each value-based price ceiling*”.

It was agreed that there are a number of sources of uncertainty in any pharmacoeconomic analysis. One member noted that clinical uncertainty is typically the primary source of uncertainty when CADTH considers new medicines, particularly for rare conditions. There are also uncertainties in the incremental costs associated with new medicines.

Furthermore, since the supply-side threshold requires empirical estimation, it will inevitably be uncertain. For example, the UK research which estimated a supply-side threshold reported a probability distribution in addition to a point estimate.¹⁰

As noted in the Conceptual Framework, any uncertainty in the incremental costs and benefits results in uncertainty in the ICER. The price at which the ICER is equal to the supply-side threshold is also uncertain, resulting in uncertainty in the true location of the demand curve. This, in turn, results in uncertainty in the ceiling price that is consistent with the policy objective regarding the allocation of the economic surplus between consumers and producers.

Some members noted that CADTH does not always report a point estimate for the ICER, but that a point estimate would be required for the purposes of informing a ceiling price.

Members discussed how a ceiling price might be informed when there is uncertainty around the ICER. The standard approach for considering uncertainty in economic evaluations is to use the expected values of the incremental costs and incremental benefits in order to calculate an ICER. This is the approach adopted in CADTH’s ‘Guidelines for the Economic Evaluation of Health Technologies: Canada’ (4th Edition).¹¹ This approach implicitly assumes ‘risk neutrality’, which is typically justified on the basis of the Arrow-Lind principle.²⁷

Members also debated using the upper bound of the credible interval around the ICER. Concern was raised that this approach would provide a disincentive for manufacturers to conduct research that reduces uncertainty around the ICER, since additional uncertainty would be rewarded with a higher ceiling price. It would also result in negative expected consumer surplus.

As noted in the Conceptual Framework, if the standard approach is adopted and a ceiling price is specified at which the ICER (calculated by dividing the expected incremental costs by the expected incremental QALYs) equals the expected value of the supply-side cost-effectiveness threshold, then the expected consumer surplus would be zero. (Note that the *actual* consumer surplus may be positive or negative, but the *expected* consumer surplus would be zero).

If the policy intent is to ensure that expected consumer surplus is non-negative, and if a risk-neutral position is adopted, then this would be the highest ceiling price consistent with this policy objective. Alternatively, if a risk-adverse position is adopted, then a higher or lower ceiling price is required to mitigate this risk. Raising the ceiling price may reduce the risk that a medicine is not launched, while lowering the ceiling price may reduce the risk that a medicine results in negative consumer surplus.

Since the PMPRB's risk attitude is not known, the Working Group cannot specify the most appropriate option for informing a ceiling price. Instead, the Working Group recommends that the PMPRB adopt an approach for considering uncertainty that is consistent with its risk attitude. If the PMPRB is 'risk-neutral', this requires that the ceiling price be informed by the expected values of the incremental costs and QALYs for the medicine and the expected value of the supply-side cost-effectiveness threshold. If the PMPRB is not 'risk-neutral', then consideration should be given to setting a ceiling price that is higher or lower than that under risk neutrality, given the policy intent.

The following *potential* recommendation was put to a vote of the Working Group:

4.3: The Working Group recommends that the PMPRB adopt an approach for considering uncertainty that is consistent with its risk attitude. If the PMPRB is 'risk-neutral', this requires that the ceiling price be informed by the expected values of the incremental costs and QALYs for the medicine and the expected value of the supply-side cost-effectiveness threshold. If the PMPRB is not 'risk-neutral', then consideration should be given to setting a ceiling price that is higher or lower than that under risk neutrality, given the policy intent.

Members voted **10 in favour** and **2 against** this potential recommendation.

This was therefore **adopted** as a formal recommendation of the Working Group.

4.3.3 Value of information analysis

In conventional pharmacoeconomics, the expected loss in consumer surplus that results from uncertainty is estimated using 'value of information' (VOI) analysis.

Since the focus of conventional pharmacoeconomic analysis is making a yes/no decision regarding adoption of a new medicine, conventional VOI analysis considers the expected loss associated with making the 'wrong' decision (e.g. approving a medicine that would otherwise have been rejected, or *vice versa*).

In the context of the PMPRB using 'pharmacoeconomic value' as a factor when considering the ceiling price for a new medicine, the expected loss as a result of uncertainty comes not from making the 'wrong' yes/no decision, but from setting the 'wrong' ceiling price. One member of the Working Group (Dr Christopher McCabe) circulated a technical note (Appendix 2.2) and gave a presentation (Appendix 2.4) outlining how uncertainty can be considered in this context. The Conceptual Framework built upon a number of the ideas outlined by Dr McCabe.

As noted in the Conceptual Framework, in many cases the expected impact upon consumer surplus of setting the 'wrong' ceiling price as a result of uncertainty is zero. This is the case if the medicine is still launched at a ceiling price coinciding with the *expected* demand curve, or if the medicine would *not* have launched even at a ceiling price coinciding with the *actual* demand curve. However, in cases where the medicine *would* have launched at a ceiling price coinciding with the *actual* demand curve, but does *not* launch at a ceiling price coinciding with the *expected* demand curve, uncertainty results in an expected loss in economic surplus.

In principle, the PMPRB could use VOI analysis to estimate this expected loss in economic surplus, and hence the value associated with obtaining additional sample information for one or more uncertain parameters. The results of these analyses could then be used to apply a reduction to a medicine's ceiling price to reflect the diminished expected pharmacoeconomic value as a result of uncertainty.

Conducting such VOI analyses would require an understanding of the location of the supply curve, since this is required to estimate the expected loss in economic surplus. As noted in the Conceptual Framework, in practice the location of the supply curve is unknown. Although the supply curve could be modelled with a probability distribution in order to permit VOI analysis to take place, methods for estimating the parameters of such a distribution are undeveloped.

As a result of these unresolved challenges, the Working Group does not make a recommendation on whether to use VOI analysis at the present time.

5: Perspectives

5.1 Terms of Reference

Within this area of focus, the Terms of Reference required the Working Group to examine and make recommendations with respect to the following considerations and questions:

Options to account for the consideration of a public health care system vs societal perspective, including the option of applying a higher value-based price ceiling in cases where there is a 'significant' difference between price ceilings under each perspective.

How to define a 'significant' difference in price ceilings between each perspective.

5.2 Policy Intent

Two months into the Working Group's deliberations, the PMPRB informed the Working Group that a **public health care system** perspective "*needs to be used to meet the policy objective of the [Regulatory Impact Analysis Statement]*".

5.3 Summary of Deliberations

5.3.1 Acknowledgement of policy intent

Two months into the Working Group's deliberations, the PMPRB informed the Working Group that it had come to the view that a public health care system perspective *"needs to be used to meet the policy objective of the [Regulatory Impact Analysis Statement]"*.

The PMPRB noted that, in coming to this view, it had benefited from the Working Group's discussions with respect to this area of focus.

Given this intervention from the PMPRB, the Working Group did not vote on any potential recommendations for this area of focus. Instead, the Working Group acknowledges that the policy intent is to adopt the perspective of Canada's public health care systems.

5.3.2 Considerations on the choice of perspective

Prior to the PMPRB's intervention to clarify the policy intent, the Working Group discussed some of the differences between a 'public health care system' perspective and a 'societal' perspective and some of the possible implications of these differences when setting ceiling prices.

Differences between perspectives

As noted in CADTH's 'Guidelines for the Economic Evaluation of Health Technologies: Canada' (4th Edition, pp.29-31), there are differences between the costs and outcomes considered under a 'public health care system' and those considered under a 'societal' perspective.¹¹

A 'public health care system' perspective only considers costs borne by the public health care payer, and the only outcomes considered are health effects relevant to patients and caregivers.

A 'societal' perspective also considers costs that fall on private insurers (e.g. medicines that are not covered by the public payer), other government sectors (e.g. social services and affordable housing), and patients or caregivers (e.g. out-of-pocket payments and travel costs). In addition, a societal perspective considers productivity costs (e.g. due to reduced working capacity or absence from work) and broadens the consideration of outcomes to include non-health effects relevant to patients and caregivers (e.g. better educational achievements).

Private insurers and out-of-pocket payers

Industry members on the Working Group expressed concern that, under a health care system perspective, costs borne by private insurers and out-of-pocket payers would not be taken into account. These members also argued that the willingness-to-pay of some private payers is higher than that of public payers, which would not be taken into account through consideration

of a supply-side cost-effectiveness threshold. It was further argued that savings to private payers through a lower ceiling price may not be passed on to individuals or employers.

In support of this position, some members noted that the willingness-to-pay of private payers may be better reflected by estimates of a 'demand-side' cost-effectiveness threshold rather than a supply-side threshold. As outlined in the IHE report, there are reasons to expect that a demand-side cost-effectiveness threshold would be higher than a supply-side threshold.

In response, one member argued that it is not meaningful to consider the willingness-to-pay of private payers in isolation from the willingness-to-pay of public payers, on the basis that the market for private payers could not exist in its present state without a sustainable public health care system. According to this member, it is therefore reasonable for the PMPRB to set a ceiling price that ensures the sustainability of the public health care system, even if this is lower than a ceiling price based on the willingness-to-pay of private payers.

One member supported a societal perspective on the basis that the PMPRB should account for *"the many rare disease patients who rely on alternatives to the public health care system"*.

Problems with a societal perspective

A number of members discussed problems with the consideration of a societal perspective.

One member suggested that adopting a societal perspective, rather than a public health care system perspective, results in *"increased uncertainty with no real impact"*. Another member argued that adopting a societal perspective implies that policy makers are willing to trade health benefits for other societal benefits, which may not be the case.

Several members expressed concern with the consideration of productivity costs that would be made under a societal perspective. Some cited the technical difficulty of estimating productivity costs and the additional uncertainty that results. Other pointed out ethical concerns, including the potential for productivity to be valued less for those with lower earning power, including women and the retired, which may be considered discriminatory.

6: Market size factor

6.1 Terms of Reference

Within this area of focus, the Terms of Reference required the Working Group to examine and make recommendations with respect to the following considerations and questions:

Approaches to derive an appropriate affordability adjustment to a medicine's ceiling price based on an application of the market size and GDP factors (e.g. based on the US 'ICER' approach).

6.2 Policy Intent

The Regulatory Impact Analysis Statement includes the following statements which provide context regarding the policy intent with respect to this area of focus:

*"The addition of this [**market size**] factor in the Regulations could enable the PMPRB to develop **market impact tests** for medicines that are likely to pose **affordability challenges** for insurers due to the **market size** for the medicine. The **impact of an excessive price** is a function of both **price** and **volume**; the **larger the size of the market** for the medicine in Canada, the **greater the impact of its price**".*

*(p.8, **emphasis added**)*

*"The introduction of **GDP in Canada** and **GDP per capita in Canada** as a price regulatory factor would provide the PMPRB with measures of **ability to pay for medicines at the national and individual level**. The inclusion of this factor would allow the PMPRB to assess the **impact of a medicine's price on the finances of consumers and insurers**. It could also enable the PMPRB to develop **market impact tests** for medicines that are likely to pose **affordability challenges** for insurers due to the **market size** for the medicine."*

*(p.9, **emphasis added**)*

The Proposed Regulatory Text includes the following text:

“4.4 For the purposes of paragraph 85(1)(e) of the Act, the other factors that the Board must take into consideration to determine whether a medicine that is sold in any market in Canada after December 31, 2018 is being or has been sold at an excessive price are the following:

- A. the **pharmacoeconomic value** in Canada of the medicine and that of other medicines in the same therapeutic class;*
- B. the **size of the market** for the medicine in Canada and in countries other than Canada; and*
- C. the **gross domestic product in Canada** and the **gross domestic product per capita in Canada.**”*

(p.24, emphasis added)

The PMPRB Guidelines Scoping Paper includes the following statement which provides context regarding the policy intent with respect to this area of focus:

*“The second part of the test would assess whether a drug that meets the cost effectiveness threshold should have its **price further adjusted** because of its **expected impact on payers within the first three to five years from launch** (assuming appropriate clinical utilization and no rationing of care). This test would consider the **anticipated market size of the new drug against GDP growth**, with the latter serving as a rough proxy for **how much Canadian consumers can afford to pay for the new patented drugs that come to market on an annual basis**. The test could also be used to allow a **price adjustment upward** in instances where a drug has a **very high opportunity cost but very small market impact due to the extreme rarity of the condition it is indicated to treat.**”*

(p.6, emphasis added)

*“The fifth and final part of the new framework would involve the **periodic “re-benching”** of drugs to ensure that previous determinations of potential excessive pricing and/or price ceilings remain relevant in light of **new indications (resulting in a change of market size) or changes in market conditions**. Depending on the nature of the change, the re-benching process could result in a **decrease or increase in ceiling price.**”*

(p.7, emphasis added)

The PMPRB Framework Modernization Presentation includes the following statements which provide context regarding the policy intent with respect to this area of focus:

*“Drugs that are expected to have a **significant market size and impact on the healthcare system** will have a **lower ceiling price** to deter rationing.”*

*(p.7, **emphasis added**)*

The PMPRB Framework Modernization Presentation includes the following slides which provide context regarding the policy intent with respect to this area of focus:

Part III: MRP for Category 1 drugs (continued)

- Step 2: application of market size and GDP factors
 - A Category 1 drug that meets the applicable \$/QALY ceiling may still face an adjustment in price if the application of the market size and GDP factors raise affordability concerns.
 - Using new drug contribution to GDP and GDP growth over the last five years, the PMPRB is estimating a threshold of \$XM per new drug.
 - New Category 1 drugs with an estimated market size that exceeds this threshold within any of its first five years of sale will require further price adjustments.
 - The adjustment would see the MRP reduced by a certain percentage discount which would increase as the expected market size increases (see next slide).
 - The market size threshold would also increase annually based on GDP growth and/or CPI.

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Application of new factors to Category 1 drugs – potential thresholds

Type of review	\$/QALY target to set MRP	Market impact adjustment
Baseline New Drug (market size up to \$20M)	\$60K	N/A
“Premium” New Drug (e.g. high burden, EDRD, significant absolute QALY gain)	\$90K to \$150K	N/A
High Impact New Drug (market size over \$20M)	\$60K	10% reduction on MRP for each additional \$10M market size (to 50% maximum)

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6.3 Summary of Deliberations

The Working Group noted that the *Proposed Regulatory Text* includes separate consideration of the pharmacoeconomic value, market size, and GDP factors. The ‘affordability adjustment’ that the Working Group was tasked with considering would therefore be applied separately from the consideration of ‘pharmacoeconomic value’.

6.3.1 Implications for consumer and producer surplus

The proposed market size adjustment includes a potential upwards ceiling price adjustment for medicines with small market size and, independently, a potential downwards ceiling price adjustment for medicines with large market size.

As shown in the Conceptual Framework, the first of these adjustments would have the effect of increasing the producer surplus, at the expense of consumer surplus, for medicines with small market size. The second of these adjustments would increase the consumer surplus, at the expense of producer surplus, for medicines with large market size.

An additional implication of the first adjustment is that, by increasing the profitability of medicines with small market size, this might result in greater access to such medicines. The potential for this is demonstrated in Figure 13B of the Conceptual Framework. This adjustment may therefore provide a means for mitigating the concerns expressed by one member regarding the potential impact of a lower ceiling price on access to orphan drugs (see section 2.3.7).

Since the desired allocation of the economic surplus among consumers and producers is a matter for policy makers, the Working Group does not take a position on the appropriate magnitude of any proposed market size adjustments. Instead, the Working Group recommends that the PMPRB consider the implications of any proposed market size adjustments for the allocation of the economic surplus, and ensure that these are consistent with the policy intent.

The following *potential* recommendation was put to a vote of the Working Group:

6.1: The Working Group recommends that the PMPRB consider the implications of any market size adjustments for the allocation of consumer and producer surplus, and ensure that these are consistent with the policy intent.

Members voted **12 in favour** and **0 against** this potential recommendation.

This was therefore **adopted** as a formal recommendation of the Working Group.

6.3.2 Potential incentives and disincentives

The Working Group discussed several potential incentives and disincentives associated with implementation of a market size adjustment.

It was noted that the estimated market size of a medicine at launch is uncertain. A market size adjustment based on a medicine's *estimated* market size might therefore result in a downwards adjustment to the ceiling price for a medicine which does not ultimately achieve a large market size. Conversely, a downwards adjustment might *not* be applied to a medicine that unexpectedly achieves a large market size. To minimize any resulting disincentives, the market size adjustment would ideally be applied to *actual* market size rather than expected market size.

If the reduction in ceiling price for medicines with large market size is large, then manufacturers may be incentivized to reduce the quantity supplied so as to avoid the reduction in the ceiling price. As demonstrated in the Conceptual Framework, this risk may be particularly acute if the medicine in question has multiple indications, and if pricing across all indications is based upon the least cost-effective indication. This is because this pricing approach may already provide an incentive for manufacturers to avoid launching in one or more indications, and the addition of a market size adjustment may exacerbate this risk.

By providing a higher ceiling price for medicines with low market size, a market size adjustment might also relatively incentivize the development of such medicines. Over time, a reduction in medicines with large market size and an increase in medicines with small market size might result in progressively smaller gains and progressively larger losses in consumer surplus.

The following *potential* recommendation was put to a vote of the Working Group:

6.2: The Working Group recommends that the PMPRB consider the potential incentives and disincentives that might result from the application of any market size adjustments.

Members voted **12 in favour** and **0 against** this potential recommendation.

This was therefore **adopted** as a formal recommendation of the Working Group.

6.3.3 GDP and GDP per capita

US 'ICER' approach

The Terms of Reference cited the Institute for Clinical and Economic Review (ICER) as providing a potential approach to inform an 'affordability adjustment'.

(Note that the acronym 'ICER' has been used elsewhere in this report to refer to a medicine's 'incremental cost-effectiveness ratio', which is the more common usage of this acronym. Within this section only, 'ICER' will be used to refer to the Institute for Clinical and Economic Review).

One member reached out to Dr Dan Ollendorf, former Chief Scientific Officer at ICER, who provided a copy of his submission to Health Canada during the consultation period on the proposed amendments. On behalf of ICER, Dr Ollendorf noted that *"we are supportive of the PMPRB's efforts to better align pricing of pharmaceuticals with value"*, and that *"we applaud the PMPRB for considering amendments that provide additional focus on pricing innovative medicines according to the value they bring to individual patients, families, and the overall health system"*. However, Dr Ollendorf raised a note of caution regarding the proposed 'affordability' criteria, noting *"several technical challenges with implementing the market size factor for price setting at ICER"*. Among these, *"there was a challenge in interpreting an explicit linkage of budget impact results to a price"*, *"it proved difficult for individual decision-makers to make sense of a national budget threshold"*, and *"any explicit linkage of a threshold to price-setting required ICER to estimate what 'unmanaged' uptake would look like, which was extraordinarily difficult"*.

UK approach

During the Working Group's deliberations, it was announced that the UK's new five-year 'Voluntary Pricing and Access Scheme' for branded medicines, which came into force on 1 January 2019, includes a 2% cap on nominal annual growth of the total medicines bill.

Using GDP to update thresholds

The Working Group discussed how any thresholds specified for the criteria used to classify medicines as 'Category 1', as well as any supply-side threshold specified by the PMPRB, may need to be periodically revised in response to changes in GDP and GDP per capita over time.

It was noted that the supply-side threshold for any specific province or territory is a function of the budget for the respective health care system, in addition to a number of other factors.⁸ A change in GDP or GDP per capita over time would therefore be expected to have an indirect impact upon the supply-side threshold through a change in the size of the health care budget. It follows that the supply-side threshold should not be adjusted directly to account for changes in GDP or GDP per capita; rather, it should be recalculated periodically to reflect changes in the

size of provincial and territorial health care budgets and the marginal productivity of health care services that face displacement from the adoption of new medicines.

The following *potential* recommendation was put to a vote of the Working Group:

6.3: The Working Group recommends that the PMPRB periodically reconsider any specified thresholds in response to changes in GDP and GDP per capita over time, including the supply-side cost-effectiveness threshold and any thresholds for criteria used to classify medicines as 'Category 1'.

Members voted **12 in favour** and **0 against** this potential recommendation.

This was therefore **adopted** as a formal recommendation of the Working Group.

6.3.4 Considerations beyond 'pharmacoeconomic value'

The chair noted that application of both the 'market size' and 'gross domestic product' factors require considerations beyond those made in assessments of 'pharmacoeconomic value'.

Since the Working Group was primarily composed of experts in pharmacoeconomics, there may be important technical considerations for the application of these two factors that are beyond the expertise of the Working Group.

Appendix 1: Conceptual Framework

A1.1 Foreword

This Conceptual Framework was drafted by the chair prior to the final meeting of the Working Group. Its purpose was to guide the Working Group in making consistent recommendations across all six areas of focus, while respecting the policy intent and the range of views expressed by members of the Working Group throughout their deliberations.

A1.1.1 Policy intent

This framework incorporates the following components of the policy intent:

During the Working Group's deliberations, the PMPRB stated that the most appropriate perspective to adopt when considering the 'pharmacoeconomic value' factor described in Amendment 4.4(a) in the Regulations Amending the Patented Medicines Regulations is that of *Canada's publicly funded health care systems*.

The Regulatory Impact Analysis Statement (Appendix 5.1) states that the *quality-adjusted life year (QALY)*, as used in cost-utility analysis, is regarded as the "gold standard" approach to considering the economic value of new medicines.

In a July 2018 document prepared for the Working Group (Appendix 5.4), the PMPRB clarified that the purpose of the PMPRB is to ensure that patentees do not change excessive prices *during the statutory monopoly period*.

The PMPRB clarified to the Working Group that its mandate is to *protect consumers from excessive pricing*, and *not* to ensure that products are launched into the market.

A1.1.2 Deliberations of the Working Group

This framework reflects the following considerations from the Working Group's deliberations:

The Terms of Reference required the Working Group to consider potential approaches for allowing higher ceiling prices for some medicines on the basis of specific characteristics. This would require departing from the position that all QALYs have equal value, allowing for 'equity weights' (other than 1) to be applied to some QALYs but not others. Although there is an emerging body of empirical evidence, it was agreed by the Working Group that methods to apply equity weights (other than 1) are undeveloped at the present time. For the purposes of this conceptual framework, QALYs are therefore assigned equal value.

The Working Group considered several approaches for setting a single ceiling price across provinces and territories, including:

1. A ceiling price at which the medicine is 'just' cost-effective in the province or territory with the highest k (such that the ICER equals this highest k);
2. A ceiling price at which the medicine is 'just' cost-effective in the province or territory with the lowest k (such that the ICER equals this lowest k);
3. A ceiling price at which the medicine is 'just' cost-effective across Canada as a whole (such that the ICER equals a 'weighted average' of k across Canada).

Although the Working Group agreed that a different ceiling price should be specified for each indication *in principle*, concerns were raised about the feasibility of doing this in Canada at the present time. The Working Group therefore considered various approaches for setting a single ceiling price across multiple indications, including:

1. A ceiling price at which the medicine is 'just' cost-effective in the most cost-effective indication (such that the ICER equals k in this indication);
2. A ceiling price at which the medicine is 'just' cost-effective in the least cost-effective indication;
3. A ceiling price at which the medicine is 'just' cost-effective across all indications (such that a 'weighted average' of the ICER across all indications equals k);
4. A ceiling price at which the medicine is 'just' cost-effective in the first indication considered by the PMPRB (such that the ICER equals k in this indication).

A1.2 Economic principles

When considering how the price of any good ought to be determined, it is informative to consider some fundamental economic principles.

At any given price, the 'economic surplus' from a good is the sum of two parts:

- The 'consumer surplus', which is the benefit obtained by consumers because they are able to purchase the good at a price lower than their 'willingness-to-pay';
- The 'producer surplus', which is the benefit obtained by producers because they are able to sell the good at a price higher than their 'willingness-to-accept'.

A1.2.1 Standard models

Mainstream economics has a number of standard models which describe how consumers and producers behave under different market conditions, and the implications of this for the allocation of the economic surplus between consumers and producers. Among many possible models, the following are of particular relevance for the Working Group's deliberations:

1. In a perfectly competitive market, an equilibrium price arises at which there is positive consumer surplus and positive producer surplus. This is because most consumers pay a price lower than their maximum willingness-to-pay (as represented by a downwards sloping demand curve), while most producers receive a price higher than their minimum willingness-to-accept (as represented by an upwards sloping supply curve). The overall economic surplus is positive and allocated between consumers and producers.
2. In a monopolistic market with a single price, the single producer reduces output and raises its price so as to maximize the producer surplus. Consumer surplus is diminished but remains positive, since some consumers still pay a price below their willingness-to-pay. However, the overall economic surplus is diminished because reducing output results in a 'deadweight loss': some consumers are willing to pay a price above the producer's supply curve, but the producer would prefer not to supply to those consumers since greater profits arise by supplying fewer consumers at a higher price.
3. In a monopolistic market with perfect price discrimination, the producer charges a different price to each consumer so as to extract the entire economic surplus. Consumer surplus is zero, since all consumers pay a price equivalent to their willingness-to-pay. The entire overall economic surplus is retained by the producer.

In order to consider the consumer and producer surplus that might arise from the PMPRB setting a ceiling price on a new medicine, we must first specify demand and supply curves.

A1.2.2 Demand curve for a medicine

The demand curve reflects society's willingness-to-pay for the medicine in question.

It is for the PMPRB, rather than members of the Working Group, to define the components of this demand curve. The Working Group therefore defers to the policy intent when considering the relevant components of the demand curve.

During the Working Group's deliberations, the PMPRB stated that the most appropriate perspective to adopt when considering the 'pharmacoeconomic value' factor described in Amendment 4.4(a) in the Regulations Amending the Patented Medicines Regulations is that of *Canada's publicly funded health care systems*.

The Regulatory Impact Analysis Statement (Appendix 5.1) states that the *quality-adjusted life year (QALY)*, as used in cost-utility analysis, is regarded as the "gold standard" approach to considering the economic value of new medicines.

In a July 2018 document prepared for the Working Group (Appendix 5.4), the PMPRB clarified that the purpose of the PMPRB is to ensure that patentees do not change excessive prices *during the statutory monopoly period*.

In light of this policy intent, a reasonable specification of the demand curve for a new medicine is based upon the net impact upon the lifetime health of patients associated with adopting the medicine within Canada's publicly funded health care systems for the duration of the statutory monopoly period, where health is measured in QALYs and discounted to a present value.

The net impact of a new medicine upon patient health is a function of two components:

1. The gain in health experienced by patients who receive the new medicine; and
2. The loss in health experienced by other patients whose health care subsequently receives less funding than it would have done in the absence of the new medicine.

The Terms of Reference required the Working Group to consider potential approaches for allowing higher ceiling prices for some medicines on the basis of specific characteristics. This would require departing from the position that all QALYs have equal value, allowing for ‘equity weights’ (other than 1) to be applied to some QALYs but not others. Although there is an emerging body of empirical evidence, it was agreed by the Working Group that methods to apply equity weights (other than 1) are undeveloped at the present time. For the purposes of this conceptual framework, QALYs are therefore assigned equal value.

The gain in health for patients who receive the medicine is routinely calculated by CADTH and INESSS as part of their existing methods for conducting economic evaluations, and is typically denoted as ΔH (where the delta refers to ‘incremental’ and H refers to ‘health benefit’).

The loss in health experienced by other patients is commonly referred to as the ‘opportunity cost’ of funding the new medicine, although it has been argued that the true opportunity cost is greater than just this ‘displaced health’.^{28,29}

Since the patients who incur these health losses are typically unidentifiable, the standard approach for estimating the magnitude of this health loss is to divide the incremental costs of the new medicine, commonly denoted as ΔC , by a parameter reflecting the ‘shadow price’ of the relevant health care budget constraint, typically denoted as k . This latter parameter is also commonly referred to as the ‘supply-side cost-effectiveness threshold’.

For example, in the case studies provided to the Working Group by the PMPRB, it was assumed that k is \$60,000 per QALY (the empirical evidence for specifying k is considered elsewhere in this report). This implies that every additional \$60,000 in cost imposed by a new medicine upon Canada’s public health care systems results in a health loss of 1 QALY.

Assuming that there is only one indication for the new medicine, and assuming a single value of k that applies regardless of the quantity of medicine supplied (assumptions reconsidered later), the demand curve for the new medicine is a perfectly elastic horizontal line that plots the ceiling price at which the health gain from the medicine is exactly offset by the health loss, such that the net health benefit is zero. That is, the demand curve plots the ceiling price at which

$$\Delta H = \Delta C/k . \tag{1}$$

Rearranging equation (1), it follows that the demand curve plots the ceiling price at which the incremental cost-effectiveness ratio (ICER) of the new medicine is equal to k :

$$\Delta C/\Delta H = k. \tag{2}$$

For the hypothetical medicine in Figure 1, the ICER is equal to k at a ceiling price of P_1 , such that the demand curve is also plotted at this ceiling price.

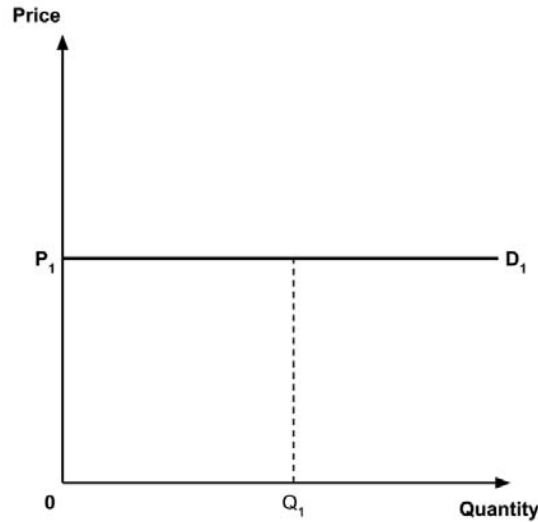


Figure 1: Demand curve for a hypothetical medicine (D_1)

The PMPRB provided the Working Group with a number of case studies (Appendix 6). For each of these case studies, the reported ‘PV Threshold Price’ is the ceiling price at which the medicine has an ICER of \$60,000 per QALY. Since \$60,000 per QALY is the PMPRB’s assumed value of k , it follows that every additional \$60,000 spent on each new medicine at the ‘PV Threshold Price’ would provide 1 additional QALY but is assumed to displace 1 additional QALY in other patients, such that the net health benefit is zero. It follows that the demand curve for the new medicine considered in each case study would be plotted at the ‘PV Threshold Price’.

Since the ceiling price at which the ICER is equal to k varies across medicines, each medicine has a different demand curve. The more cost-effective a medicine is, and hence the more QALYs produced at a given ceiling price, the higher the ceiling price at which the ICER is equal to k and the higher the demand curve (Figure 2A). Conversely, the less cost-effective a medicine is, the lower the demand curve (Figure 2B).

It follows that the developers of future medicines have two mechanisms by which they can raise the demand curve for their medicine upon launch: improve the effectiveness of the medicine (and the resulting health gain) or reduce the price (and the resulting health loss).

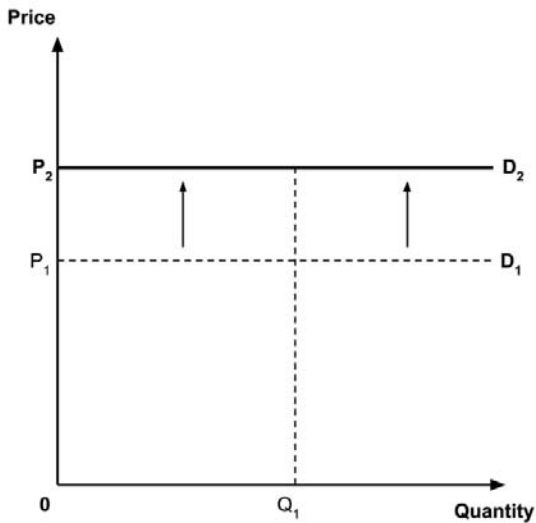


Figure 2A: Demand curve for a more cost-effective medicine (D_2)

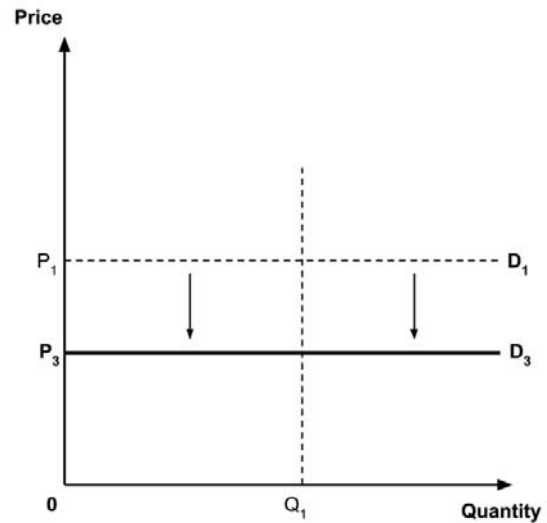


Figure 2B: Demand curve for a less cost-effective medicine (D_3)

A1.2.3 Supply curve for a medicine

The supply curve plots the lowest price that a manufacturer would be willing to accept for a medicine. This is sometimes referred to as the ‘reservation’ (or ‘reserve’) price of the medicine.

The supply curve is a function of a number of potential considerations, including the initial costs associated with developing the medicine, the marginal costs of production, and the potential implications for pricing in other jurisdictions as a result of ‘reference pricing’.

It is important to note that the supply curve in a specific jurisdiction does not necessarily reflect only the marginal costs of production or the required return on investment for the manufacturer. Due to the possibility of reference pricing, a manufacturer might be unwilling to accept a price in a specific jurisdiction, even if this covers the marginal costs of production and provides a sufficient return on investment in that jurisdiction, if this results in a lower price in one or more other jurisdictions. One means of mitigating this possibility is through the use of confidential pricing arrangements, such that the price actually paid in a specific jurisdiction is lower than the ‘list price’ used by other jurisdictions for the purpose of reference pricing. Confidential pricing arrangements may therefore be expected to lower the supply curve, since the implications for reference pricing in other jurisdictions are no longer a relevant factor.

Regardless of whether reference pricing is a relevant factor, the components of the supply curve are complex. Furthermore, compared to the components of the demand curve (such as k),

relatively little empirical research has been conducted into the components of the supply curve, with existing research focused primarily on estimating the costs associated with research and development (rather than the expected reservation price). As a result of this asymmetry, the supply curve for each new medicine is highly uncertain. For the purposes of this framework, the medicine's supply curve will therefore be treated as unknown (and plotted as a dashed line).

Despite being unknown, we may reasonably expect the supply curve for a medicine to have the following basic properties:

1. A relatively high intercept on the vertical axis, reflecting the substantial initial costs associated with researching and developing the medicine;
2. A downwards slope, reflecting a declining per-patient cost of supplying the medicine as the quantity supplied increases. This declining per-patient cost arises from the ability to spread the initial costs of research and development across a greater number of patients, and also potential economies of scale in the production of the medicine.

Since initial research and development costs and production costs vary across medicines, each medicine would be expected to have a different supply curve.

For example, recent empirical work found that the initial development costs for an orphan drug (with a small patient population, resulting in a relatively small quantity supplied) are \$291m USD (average capitalized clinical cost), compared to \$412m USD for a non-orphan drug.³⁰

Other recent work has found that the research and development costs associated with a new orphan drug are smaller than those for a non-orphan drug, but, given the smaller patient population, a higher per-patient price is required for orphan drugs to sustain a similar return on investment than non-orphan drugs.³¹

Figure 3 plots possible supply curves for two hypothetical medicines. Although both medicines are assumed to have large development costs, the first medicine (represented by supply curve S_1) will be supplied at a lower price, for any given quantity, than the second medicine (represented by supply curve S_2). For example, at a given quantity, Q_1 , the manufacturer of the first medicine is willing to accept a price of P_4 , whereas the manufacturer of the second medicine requires a higher price of P_5 . Among many other possible reasons, this might be due to the first medicine having relatively lower marginal costs of production.

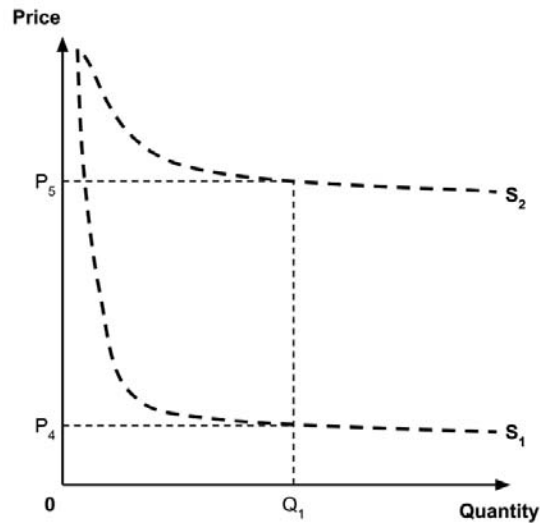


Figure 3: Supply curves for two hypothetical medicines, with relatively low (S_1) and high (S_2) marginal costs of production

A1.2.4 Economic surplus

The demand and supply curves may be used to consider the ‘economic surplus’ that results from adoption of a new medicine and, at any given ceiling price, the distribution of this economic surplus between consumers (patients) and producers (the manufacturers of new medicines).

When demand and supply curves are plotted on the same figure, the economic surplus is illustrated by the area of the region below the demand curve and above the supply curve, minus any area above the demand curve but below the supply curve, and bounded between the vertical axis and the quantity of medicine adopted.

For example, Figure 4A plots the demand (D_1) and supply (S_1) curves for a medicine with a relatively low supply curve. At a quantity of Q_1 , the economic surplus is positive and illustrated by the area of region 2 minus the area of region 1.

Figure 4B, by contrast, plots the demand (D_1) and supply (S_2) curves for a medicine with a relatively high supply curve. Since the supply curve lies entirely above the demand curve, adopting this medicine at a quantity of Q_1 would result in a negative economic surplus, as illustrated by the area of region 3.

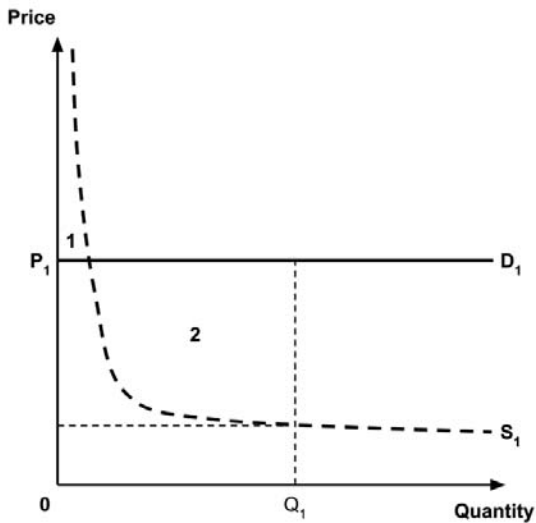


Figure 4A: Demand and supply curves for a medicine with a relatively low supply curve, resulting in a positive total economic surplus

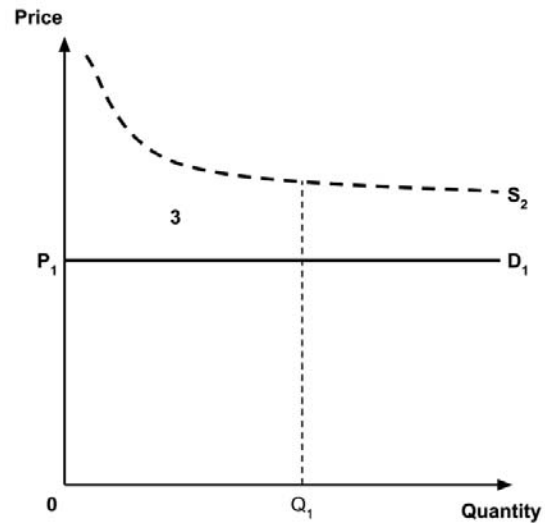


Figure 4B: Demand and supply curves for a medicine with a relatively high supply curve, resulting in a negative total economic surplus

A1.2.5 Defining consumer and producer surplus

Given the policy intent, the ‘consumer surplus’ arising from adoption of a new medicine reflects the net health benefit (in QALYs) for patients within Canada’s public health care systems.

The ‘producer surplus’, meanwhile, reflects profits for the manufacturers of new medicines.

A1.2.6 Allocating a positive economic surplus

How the economic surplus might be allocated among ‘consumers’ (patients) and ‘producers’ (manufacturers) depends upon whether this overall economic surplus is positive or negative.

If the economic surplus is positive, as in Figure 5A, then there is a range of possible ceiling prices at which consumer and producer surplus are both positive, such that adoption of the new medicine would provide a net benefit to patients and also the manufacturer.

The upper bound of this range is a ceiling price corresponding to the demand curve (P_1 in Figure 5A), at which the ICER is k . At this ceiling price, the entirety of the economic surplus (illustrated by the area of region 2 minus the area of region 1) is allocated to the producer, such that the consumer surplus is zero. This is analogous to the allocation of consumer and producer

surplus that would arise in a conventional model of monopoly with perfect price discrimination (in which the producer extracts the entire economic surplus).

The lower bound of this range is a ceiling price at which producer surplus is zero (P_6 in Figure 5B). At this ceiling price, the ICER is below k and consumer surplus is positive, illustrated by the combined area of regions 4 and 5. Producer surplus is zero, illustrated by the area of region 6 minus the combined area of regions 1 and 4. Note that the overall economic surplus remains the same as in Figure 5A, and is equivalent to the combined area of regions 1, 5 and 6 only (since area 4 constitutes both a benefit for consumers and a loss for producers).

A ceiling price above P_1 (so the ICER exceeds k) would result in negative consumer surplus (such that the new medicine would diminish population health), and a ceiling price below P_6 would result in negative producer surplus (such that the new medicine is not profitable).

It follows that only a ceiling price between P_1 and P_6 in Figure 5B would result in both positive consumer surplus and positive producer surplus. At any ceiling price within this range, the ICER of the new medicine is lower than k . Compared to the allocation of consumer and producer surplus which arises when the ceiling price corresponds to the demand curve (such that the ICER is exactly k), this allocation is closer to that which would arise in a conventional model of a competitive market (in which consumer and producer surplus are both positive).

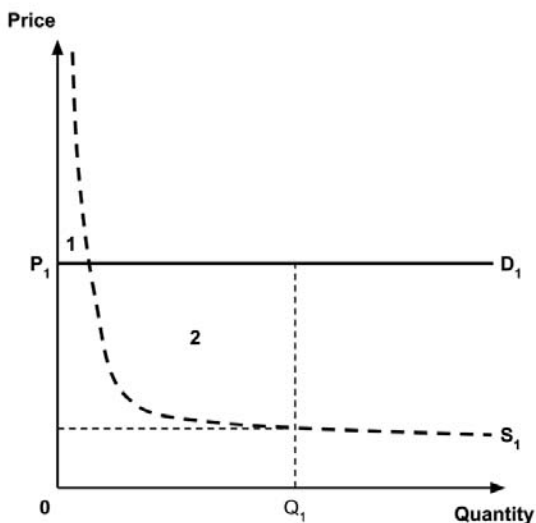


Figure 5A: At a price of P_1 , the entire economic surplus is allocated to the producer (region 2 minus region 1)

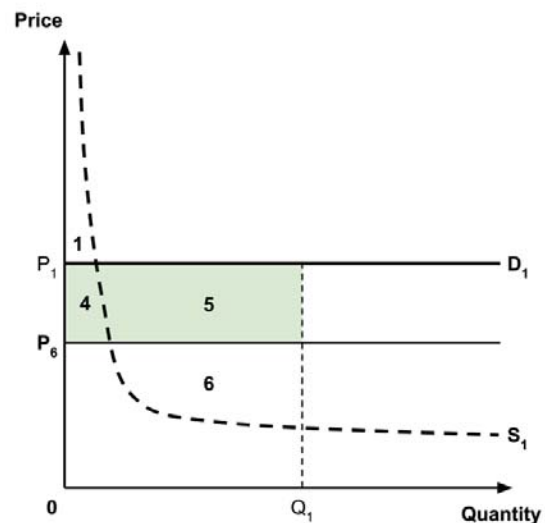


Figure 5B: At a price of P_6 , the entire economic surplus is allocated to the consumer (regions 4 and 5)

A1.2.7 Allocating a negative economic surplus

If the economic surplus is negative, as in Figure 4B, then there are no possible ceiling prices at which both consumer and producer surplus are positive.

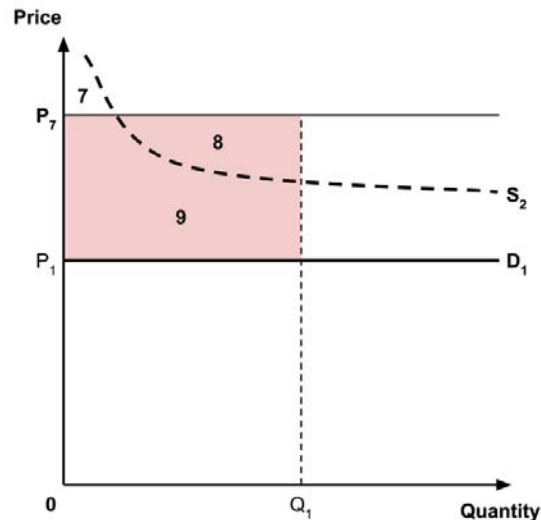


Figure 6: Where the supply curve lies above the demand curve, producer surplus cannot be positive unless consumer surplus is negative

Although a higher ceiling price can be sought for the medicine at which producer surplus is positive, this will result in negative consumer surplus. The consequence of a negative consumer surplus is that other patients will incur a greater loss in health than will be gained by the patients who receive the new medicine, in turn diminishing population health.

For example, in Figure 6, a ceiling price of P_7 results in a positive producer surplus, as illustrated by the area of region 8 minus the area of region 7. However, consumer surplus is negative, as illustrated by the combined area of regions 8 and 9. Attempts to avoid this negative consumer surplus by lowering the ceiling price will also result in negative producer surplus.

The potential for the supply curve to lie above the demand curve is a particularly important consideration for medicines that are supplied to relatively few patients, such as orphan drugs, for which the supply curve may be more likely to be higher than the demand curve at the relevant quantity.

A1.3 Pricing across provinces and territories

The IHE report considered the various determinants of k .²

A key determinant is the size of the relevant health care budget, with larger per-capita health care budgets resulting in higher values of k (all else equal).

Other determinants include the marginal productivity of existing health care activities that might experience reduced funding or displacement if a new medicine is adopted.⁸

A1.3.1 Variations in 'k' across provinces and territories

Since provinces and territories in Canada have some autonomy in setting health care budgets and prioritizing spending, it follows that k would be expected to vary by province and territory.

This is supported by the empirical work by Ochalek *et al.* (2018), which reported varying estimates of the marginal 'cost per DALY averted' across provinces and territories.¹ Using data from Claxton *et al.* (2017), this report found higher estimates in the territories (ranging from \$30,633 per DALY averted in Yukon to \$52,191 per DALY averted in the Northwest Territories), and lower estimates across the provinces (ranging from a low of \$16,425 per DALY averted in Prince Edward Island to a high of \$26,060 per DALY averted in Alberta).

Note that, although these estimates were reported in terms of marginal 'cost per DALY averted', similar variation in estimates would be expected if these were instead reported in terms of marginal 'cost per QALY gained', which is how k should be specified given the policy intent.

A1.3.2 Implications for the opportunity cost of new medicines

An important implication of this variation in k is that the opportunity cost of adopting a new medicine would be expected to differ across provinces and territories. The lower k is in any province or territory, the greater the expected opportunity cost associated with adopting a new medicine (in terms of health forgone by other patients).

For example, based upon the report by Ochalek *et al.* (2018), every additional \$1m spent on new medicines in Prince Edward Island would have an opportunity cost of approximately 60 DALYs, but every additional \$1m spent on new medicines in Alberta would have a smaller opportunity cost of approximately 40 DALYs. All else equal, the net health benefit of any new medicine would therefore be expected to be smaller in Prince Edward Island than in Alberta.

A1.3.3 Implications for the demand curve

Since the demand curve plots the ceiling price at which the ICER of the new medicine is equal to k (equation 2), it follows that the demand curve will be higher in provinces and territories with larger estimates of k .

For example, based on the empirical work by Ochalek *et al.* (2018), we might expect the lowest demand curve in Prince Edward Island, the highest provincial demand curve in Alberta, and the highest demand curve overall in the Northwest Territories.

The width of each demand curve (the quantity demanded) would also be expected to differ across provinces and territories, since the number of patients receiving each new medicine will vary due to differences in population size and demographics.

A1.3.4 Approaches for setting a single ceiling price

The Working Group considered several approaches for setting a single ceiling price across provinces and territories, including:

1. A ceiling price at which the medicine is 'just' cost-effective in the province or territory with the highest k (such that the ICER equals this highest k);
2. A ceiling price at which the medicine is 'just' cost-effective in the province or territory with the lowest k (such that the ICER equals this lowest k);
3. A ceiling price at which the medicine is 'just' cost-effective across Canada as a whole (such that the ICER equals a 'weighted average' of k across Canada).

Figures 7A to 7D demonstrate the implications of each of these approaches using a simplified model of a new medicine provided to patients across two provinces. In this model, 'Province A' has a higher k than 'Province B', such that the ceiling price at which the ICER of the medicine equals k in 'Province A' is P_8 . Given its size and demographics, 'Province A' demands a quantity of medicine Q_2 . 'Province B' demands a smaller quantity, $Q_3 - Q_2$, and has a lower k than 'Province A', such that the ICER would equal k for this province at a ceiling price of P_9 .

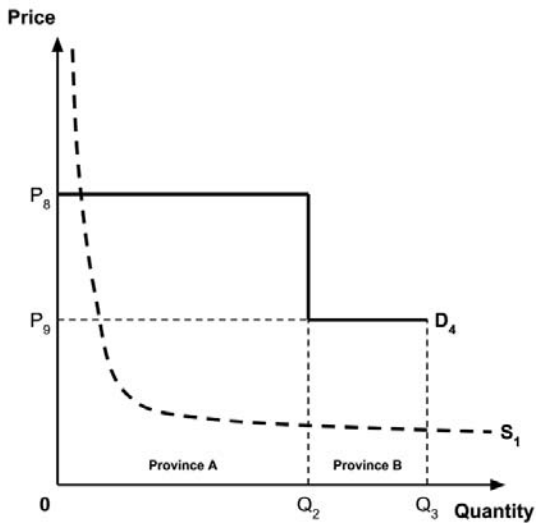


Figure 7A: The demand curve for a medicine across two provinces

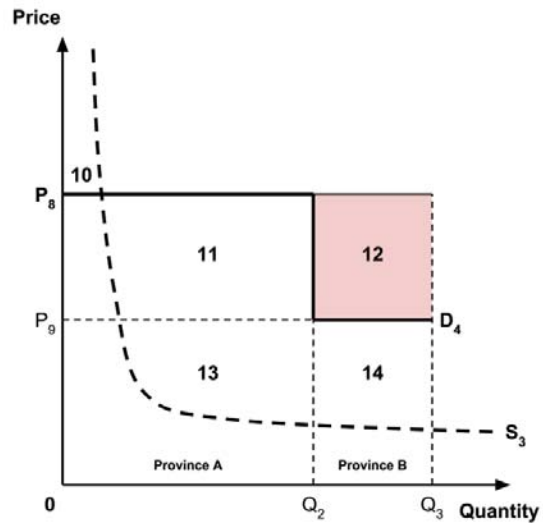


Figure 7B: Under the first approach (ceiling price P_8), consumer surplus is negative in 'Province B' and zero in 'Province A', so negative overall

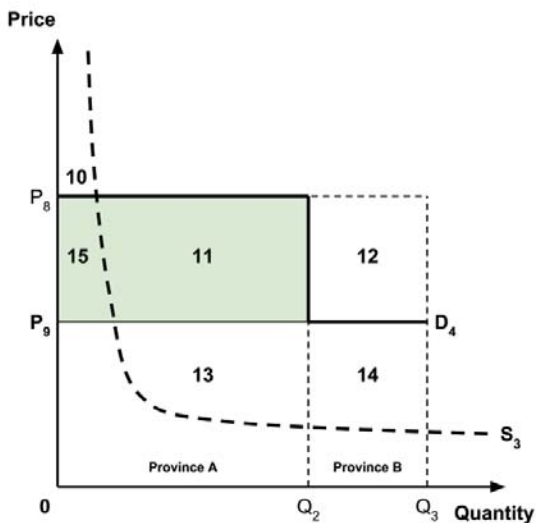


Figure 7C: Under the second approach (ceiling price P_9), consumer surplus is positive in 'Province A' and zero in 'Province B', so positive overall

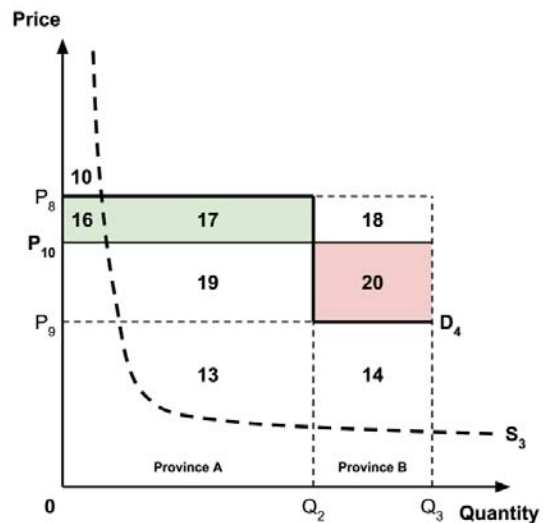


Figure 7D: Under the third approach (ceiling price P_{10}), consumer surplus is positive in 'Province A', negative in 'Province B', and zero overall

Approach 1: Set a ceiling price according to the highest k

Under the first approach considered by the Working Group, the ceiling price of the new medicine would be set at P_8 in both provinces (Figure 7B).

This would result in no consumer surplus in 'Province A' (since the ceiling price corresponds exactly to the demand curve), but negative consumer surplus in 'Province B' (as illustrated by the area of region 12) since the ceiling price lies above the demand curve. It follows that the total consumer surplus (across both provinces) would be negative, such that population health is diminished.

At this ceiling price, the producer surplus is illustrated by the combined area of regions 11, 12, 13 and 14, minus the area of region 10.

Approach 2: Set a ceiling price according to the lowest k

Under the second approach, the ceiling price would be set at P_9 in both provinces (Figure 7C).

This would result in a positive consumer surplus in 'Province A' (the combined area of regions 11 and 15), and no consumer surplus in 'Province B' (since the ceiling price corresponds exactly to the demand curve), such that the total consumer surplus is positive.

The producer surplus would be lower than under the first approach, as illustrated by the combined area of regions 13 and 14, minus the combined area of regions 10 and 15.

Approach 3: Set a ceiling price according to a weighted average of k

Under the third approach, the ceiling price would be set between P_8 and P_9 such that the total consumer surplus (across both provinces) is zero. In this example, this requires setting a ceiling price of P_{10} (Figure 7D).

At a ceiling price of P_{10} , the positive consumer surplus in 'Province A' (combined area of regions 16 and 17) is exactly offset by the negative consumer surplus in 'Province B' (area of region 20).

The producer surplus is lower than under the first approach but greater than under the second approach, as illustrated by the combined area of regions 13, 14, 19 and 20, minus the combined area of regions 10 and 16.

A1.3.5 Implications of a supply curve above the demand curve

In Figures 7A to 7D, the supply curve for the new medicine was plotted such that producer surplus is positive at all ceiling prices between P_8 and P_9 . However, for medicines with a higher supply curve, it is possible that negative producer surplus might arise at some ceiling prices within this range.

For example, Figure 8A plots a supply curve (S_4) which lies entirely above P_9 . Under the first approach considered above (pricing at P_8), producer surplus would be positive (the combined area of regions 22 and 23, minus the area of region 21), but the consumer surplus would be negative (as in Figure 7B). However, under the second approach (pricing at P_9), the medicine would have negative producer surplus (the combined area of regions 21, 24 and 25).

For medicines with a particularly high supply curve, negative producer surplus might arise at *all* ceiling prices between P_8 and P_9 .

For example, Figure 8B plots a supply curve (S_5) which lies entirely above P_8 . It follows that the medicine would have negative producer surplus under all of the approaches considered above, including under the first approach with a ceiling price of P_8 (where the negative producer surplus is illustrated by the area of region 26). In this case, no ceiling price exists which provides both positive consumer and producer surplus, as would arise in a competitive market.

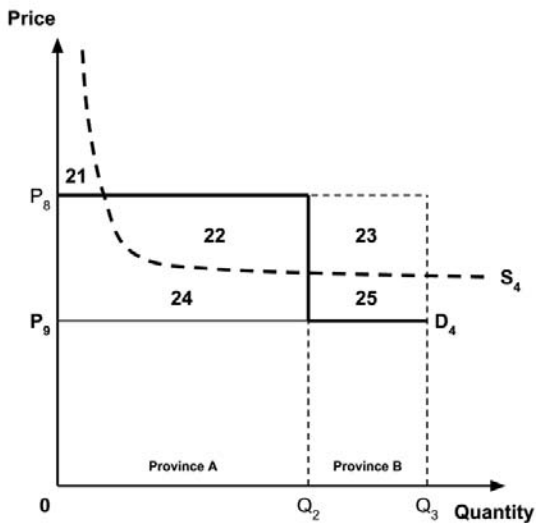


Figure 8A: With a higher supply curve (S_4), the medicine is profitable at price P_8 but unprofitable at price P_9

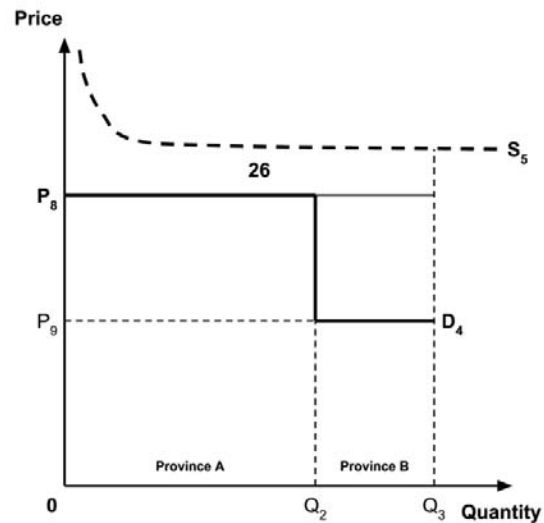


Figure 8B: With an even higher supply curve (S_5), the medicine is unprofitable even at price P_8

A1.3.6 Policy implications

The most desirable approach for setting a single ceiling price across Canada depends upon the policy intent.

Note that it is not the role of the Working Group to specify the policy intent. While the implications of some potential policy objectives are considered below, this should not be construed as an endorsement by the Working Group of any particular policy objective. Also note that this analysis is not exhaustive: there are other potential policy objectives and approaches for setting a ceiling price across provinces and territories.

Potential policy objective 1

If the policy maker desires that new medicines *do not diminish population health across Canada as a whole*, such that overall consumer surplus is at least zero, then the first approach considered above is inconsistent with this policy objective. This is because this approach results in diminished population health (negative consumer surplus) in all provinces and territories except that with the highest k (in which consumer surplus is zero), resulting in diminished population health (negative consumer surplus) overall.

The second approach comfortably satisfies this policy objective (since it results in positive overall consumer surplus), while the third approach only just satisfies this policy objective (since it results in an overall consumer surplus of zero).

It follows that the ceiling price that arises under the third approach (P_{10} in Figure 7D) is the maximum ceiling price that would be consistent with this policy objective. At this ceiling price, overall consumer surplus is zero, analogous to the consumer surplus arising in a standard model of a monopoly with perfect price discrimination.

Potential policy objective 2

If the policy maker instead desires that new medicines *do not diminish population health within any province or territory*, then both the first and third approaches are inconsistent with this policy objective. This is because both approaches result in diminished population health (negative consumer surplus) in at least one province or territory.

The second approach would only just satisfy this policy objective, since consumer surplus is zero in the province or territory with the lowest k .

It follows that the ceiling price that arises under the second approach (P_9 in Figure 7C) is the maximum ceiling price that would be consistent with this policy objective. Provided that producer

surplus is positive, such that the new medicine is launched, overall consumer surplus is also positive.

Note that if producer surplus is negative at P_9 then it is not possible to set a ceiling price which satisfies this policy objective and provides for positive producer surplus.

Potential policy objective 3

If the policy maker wishes to set ceiling prices for new medicines so as to *maximize population health across Canada as a whole*, then consideration should be given to the location of the supply curve. Since the location of the supply curve is uncertain, this is challenging in practice.

A key assumption in the analysis below is that a medicine will not be launched if producer surplus is negative. If a medicine is not launched, the pharmacoeconomic value is zero since there is no resulting net gain in QALYs. For the pharmacoeconomic value to be positive, the medicine must be launched at a ceiling price that results in positive consumer surplus.

The PMPRB clarified to the Working Group that its mandate is to *protect consumers from excessive pricing*, and *not* to ensure that products are launched into the market.

If the supply curve is understood to be sufficiently high that the medicine would not be profitable at the ceiling price arising under the third approach (P_{10} in Figure 7D), then it is not possible to specify a ceiling price at which the medicine is profitable and improves population health.

Alternatively, if the medicine is profitable at the ceiling price arising under the third approach (P_{10} in Figure 7D), but is not profitable at the ceiling price arising under the second approach (P_9 in Figure 7C), then maximizing population health requires specifying a ceiling price somewhere between P_9 and P_{10} , such that consumer surplus is maximized subject to producer surplus being non-negative.

Finally, if the supply curve is understood to be sufficiently low that the medicine would be profitable at the ceiling price arising under the second approach (P_9 in Figure 7C), then maximizing population health requires setting a ceiling price *below* P_9 , so as to maximize consumer surplus subject to producer surplus being non-negative. However, since the true location of the supply curve is uncertain, any reduction in the ceiling price carries a risk that producer surplus might become negative, such that the medicine would not launch at all. In such circumstances, consumer surplus would be zero, whereas at a higher ceiling price of P_9 the new medicine would have launched and consumer surplus would have been positive.

A1.4 Pricing across indications

Where a medicine is available for multiple indications, this has implications for specification of the demand curve for a new medicine.

If the per-patient health gain from the new medicine is different in each indication, then the ceiling price at which the ICER is equal to k will also differ across indications.

It follows that the demand curve will generally be different for each indication, with a relatively higher ceiling price corresponding to an ICER of k for those indications in which the medicine has a relatively greater per-patient health gain.

A1.4.1 Approaches for setting a single ceiling price across indications

Although the Working Group agreed that a different ceiling price should be specified for each indication *in principle*, concerns were raised about the feasibility of doing this in Canada at the present time. The Working Group therefore considered various approaches for setting a single ceiling price across multiple indications, including:

1. A ceiling price at which the medicine is 'just' cost-effective in the most cost-effective indication (such that the ICER equals k in this indication);
2. A ceiling price at which the medicine is 'just' cost-effective in the least cost-effective indication;
3. A ceiling price at which the medicine is 'just' cost-effective across all indications (such that a 'weighted average' of the ICER across all indications equals k);
4. A ceiling price at which the medicine is 'just' cost-effective in the first indication considered by the PMPRB (such that the ICER equals k in this indication).

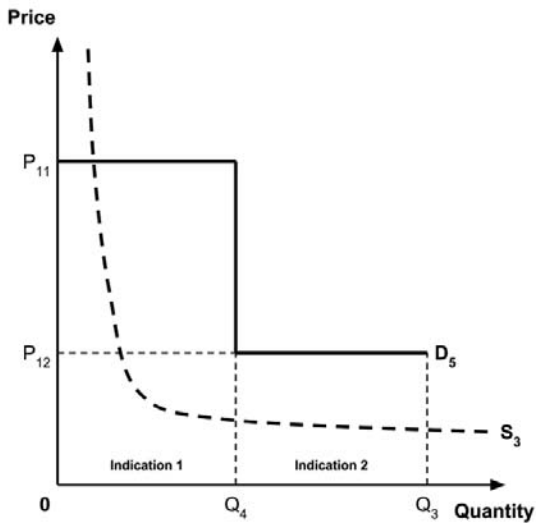


Figure 9A: The demand curve for a medicine across two indications

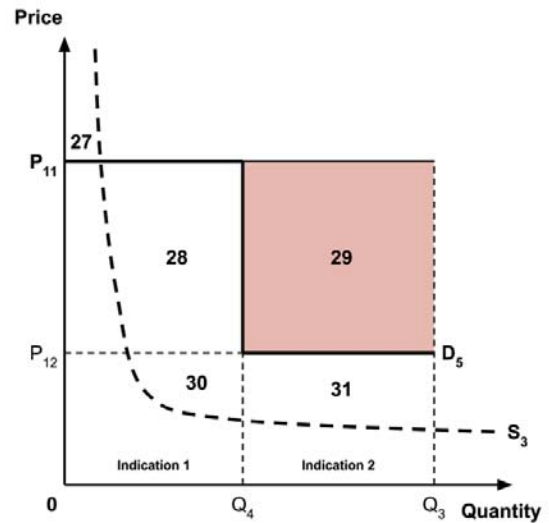


Figure 9B: Under the first approach (ceiling price P_{11}), consumer surplus is negative in 'Indication 2' and zero in 'Indication 1', so negative overall

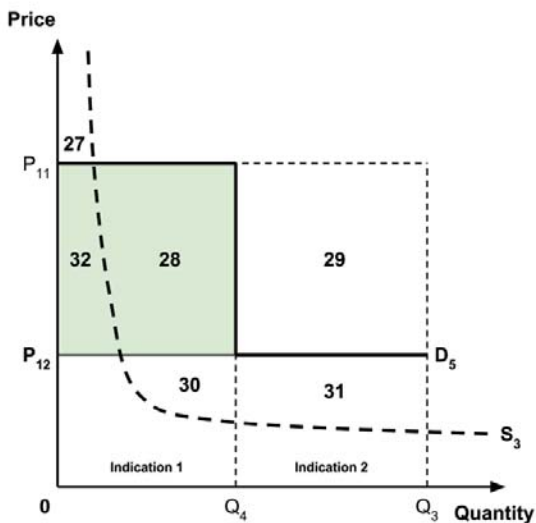


Figure 9C: Under the second approach (ceiling price P_{12}), consumer surplus is positive in 'Indication 1' and zero in 'Indication 2', so positive overall

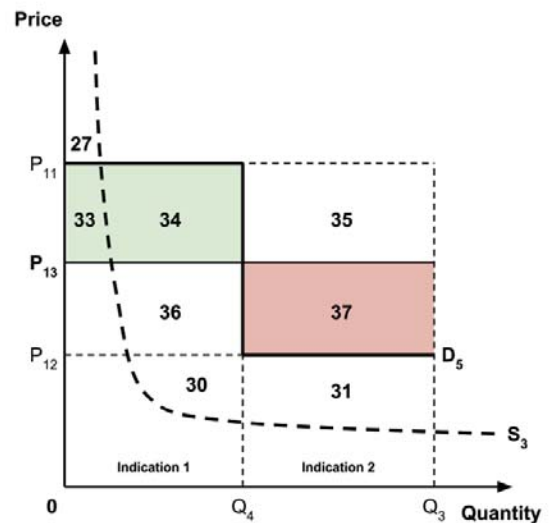


Figure 9D: Under the third approach (ceiling price P_{13}), consumer surplus is positive in 'Indication 1', negative in 'Indication 2', and zero overall

Figures 9A to 9D demonstrate the implications of each of these approaches using a simplified model of a new medicine provided to patients across two indications. In this model, the medicine is relatively more effective for patients in 'Indication 1', resulting in a larger health gain. Given this effectiveness, the ceiling price at which the ICER equals k for patients in 'Indication 1' is P_{11} . The quantity of medicine demanded by patients in 'Indication 1' is Q_4 . The medicine is relatively less effective for patients in 'Indication 2', such that the ICER equals k at a lower ceiling price of P_{12} . The quantity of medicine demanded by patients in 'Indication 2' is $Q_3 - Q_4$.

In the analysis below, it is assumed that the medicine is always launched in both indications (i.e. the manufacturer does not strategically limit launch of the medicine to only one indication). The possible implications of such strategic behaviour are considered later in this section.

Approach 1: Set a ceiling price based on the most cost-effective indication

Under the first approach considered by the Working Group, the ceiling price of the new medicine would be set at P_{11} across both indications (Figure 9B).

This would result in no consumer surplus in 'Indication 1' (since the ceiling price corresponds exactly to the demand curve), but negative consumer surplus in 'Indication 2' (as illustrated by the area of region 29) since the ceiling price lies above the demand curve. It follows that the total consumer surplus across both indications would be negative, such that population health is diminished.

At this ceiling price, the producer surplus is illustrated by the combined area of regions 28 to 31, minus the area of region 27.

Approach 2: Set a ceiling price based on the least cost-effective indication

Under the second approach, the ceiling price would be set at P_{12} in both indications (Figure 9C).

This would result in a positive consumer surplus in 'Indication 1' (regions 28 and 32), and no consumer surplus in 'Indication 2' (since the ceiling price corresponds exactly to the demand curve), such that the total consumer surplus is positive.

The producer surplus would be lower than under the first approach, as illustrated by the combined area of regions 30 and 31, minus the combined area of regions 27 and 32.

Approach 3: Set a ceiling price based on a 'weighted average' of all indications

Under the third approach, the ceiling price would be set between P_{11} and P_{12} such that the total consumer surplus (across both indications) is zero. In this example, this requires setting a ceiling price of P_{13} (Figure 9D).

At this ceiling price, the positive consumer surplus in 'Indication 1' (combined area of regions 33 and 34) is exactly offset by the negative consumer surplus in 'Indication 2' (area of region 37).

The producer surplus is lower than under the first approach but greater than under the second approach (as illustrated by the combined area of regions 30, 31, 36 and 37, minus the combined area of regions 27 and 33).

Approach 4: Set a ceiling price based on the first indication considered

Under the fourth approach, the ceiling price would be set at either P_{11} or P_{12} , depending upon which indication is first considered by the PMPRB.

This approach is the simplest to administer, since it does not require rebenching of ceiling prices in future if and when additional indications are launched.

However, because producer surplus is unambiguously greater at a ceiling price of P_{11} than P_{12} , this approach provides an incentive for the manufacturer to launch in the most cost-effective indication first (in this case 'Indication 1') to secure a higher ceiling price for future indications.

(If the manufacturer instead launches in 'Indication 2' first, then the loss in producer surplus is illustrated by the combined area of regions 28, 29 and 32 on Figure 9C.)

If manufacturers act upon this incentive and prioritize launch of the most cost-effective indication first, then overall consumer surplus will be zero within the initial indication and become negative once additional indications are launched. If manufacturers are perfectly strategic, then this approach would have the same implications for consumer surplus as Approach 1.

If manufacturers do *not* act upon this incentive, then in some cases consumer surplus from additional indications will be positive (if a less cost-effective indication is launched first) and in other cases consumer surplus from additional indications will be negative (if a more cost-effective indication is launched first). If the decision as to which indication to launch first is truly random, then a reasonable expectation would be that the *expected* consumer surplus associated with additional indications is zero, since it is equally likely to be positive or negative. This would have equivalent implications for consumer surplus as Approach 3.

It follows that this approach may be considered as lying somewhere between Approach 1 and Approach 3, with expected consumer surplus ranging between negative (if manufacturers are in any way strategic) to zero (if manufacturers are not strategic at all).

A1.4.2 Similarities to pricing across multiple provinces and territories

There are several similarities between the Working Group's considerations regarding pricing across multiple indications and those regarding pricing across multiple provinces and territories.

In both cases, the demand curve for a medicine differs across subsets of patients who receive a medicine, whether on the basis of province or territory or on the basis of disease indication. In both cases, the Working Group considered pricing according to the highest or lowest of these demand curves, or pricing according to a 'weighted average' approach. And in both cases, these various approaches resulted in very different implications for the allocation of consumer and producer surplus (with one approach resulting in negative consumer surplus, another resulting in positive consumer surplus, and a third approach resulting in zero consumer surplus).

There are, however, some distinctions. First, the reason why demand curves differ across provinces or territories (because k varies for a given ΔH) is different from why demand curves differ across indications (because ΔH varies for a given k). Second, the manufacturer may have an opportunity to behave strategically regarding the order in which indications are launched, or may choose not to launch in a specific indication at all, in order to maximize profits.

A1.4.3 Potential for strategic behaviour by manufacturers

Since manufacturers may choose not to launch in one or more indications, any approach for setting ceiling prices across indications can potentially induce strategic behaviour by manufacturers, with implications for the allocation of consumer and producer surplus.

In the earlier analysis of each of the four approaches for pricing across indications, it was assumed that the new medicine would always be launched in both indications. Under the second approach, launch of the medicine in 'Indication 2' resulted in a lower ceiling price in 'Indication 1', in turn leading to positive consumer surplus. However, if this approach were to be adopted in practice, manufacturers might strategically choose *not* to launch in 'Indication 2', resulting in a higher ceiling price for 'Indication 1', in turn leading to zero consumer surplus.

The reasons for this can be seen by considering Figure 10, which is adapted from Figure 9C. If the manufacturer launches in both indications then the ceiling price is P_{12} (based on the demand curve for 'Indication 2', the least cost-effective indication). The producer surplus is then the combined area of regions 30 and 31 *minus* the combined area of regions 27 and 32.

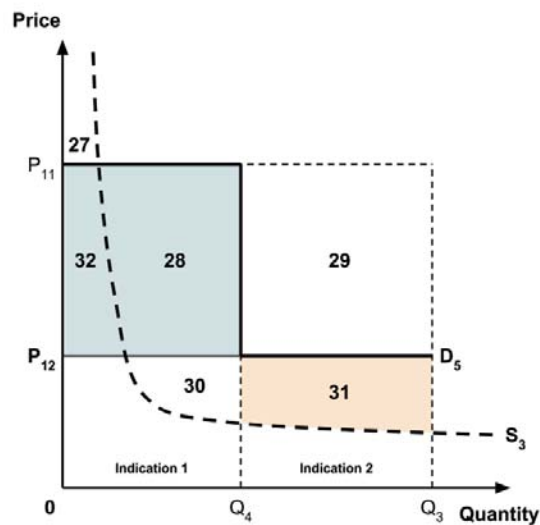


Figure 10: Under Approach 2, the manufacturer may strategically choose *not* to launch in Indication 2, thereby increasing producer surplus by the area of regions 28 and 32 *minus* region 31

However, if the manufacturer instead launches only in 'Indication 1', then this would now be the least cost-effective indication and so the ceiling price would be P_{11} . The producer surplus would now be the combined area of regions 28 and 30 *minus* the area of region 27.

It follows that, by avoiding launching in 'Indication 2', the manufacturer forgoes the producer surplus in region 31 but gains additional producer surplus in regions 28 and 32. In the example given in Figure 10, this gain in producer surplus outweighs the loss. A manufacturer wishing to maximize producer surplus would therefore strategically launch in 'Indication 1' only.

This strategic behaviour has several implications. First, it increases the producer surplus. Second, it reduces the consumer surplus (in this case to zero, although in an example with many indications the consumer surplus may be positive if the medicine still launches in two or more indications). Third, it results in a 'deadweight loss', represented by the area of region 31.

This deadweight loss arises because there is a demand for the medicine for patients in 'Indication 2', with a willingness-to-pay of P_{12} , and the manufacturer is willing to supply to these patients at a ceiling price lower than this. It follows that there is an economic surplus to be realized by providing the medicine to patients in 'Indication 2'. However, the manufacturer is unwilling to supply to these patients because, by doing so, the total surplus allocated to the manufacturer falls (since the ceiling price would fall from P_{11} to P_{12} in both indications). The potential economic surplus in region 31 is therefore not realized.

There are several potential ways to address this issue, each with positives and negatives. Applying a different ceiling price to each indication, such that the ceiling price for 'Indication 1' is independent of the ceiling price for 'Indication 2', would remove the incentive not to supply to 'Indication 2'. However, as noted earlier, members of the Working Group expressed concerns about the feasibility of implementing indication-specific pricing at the present time. Also, unless a ceiling price below the respective demand curve was applied in each indication, overall consumer surplus would be zero (analogous to that in a standard model of a monopoly with perfect price discrimination).

The policy maker might also consider applying a ceiling price higher than P_{12} if the medicine is launched in both indications. In order for this to result in positive consumer surplus overall, this ceiling price would have to be lower than P_{13} in Figure 9D (the ceiling price that arises under the third approach, in which consumer surplus is zero). Although a ceiling price between P_{12} and P_{13} would result in negative consumer surplus in 'Indication 2', there would still be positive consumer surplus overall, which might be considered preferable to the situation where the medicine is launched only in 'Indication 1' and consumer surplus is zero.

Another potential solution would be to 'penalize' the manufacturer for choosing not to launch in 'Indication 2' by setting a ceiling price below P_{11} if the medicine is launched only in 'Indication 1'. This might result in producer surplus being maximized by launching in both indications, incentivising the manufacturer to also launch in 'Indication 2'. However, if the overall producer surplus becomes negative as a result of this lower ceiling price, the manufacturer might choose not to launch the medicine in *any* indication, resulting in zero consumer surplus.

Regardless of the approach taken, if the policy maker attempts to mitigate this strategic behaviour by raising or lowering the ceiling price then a key challenge is determining how much higher or lower the ceiling price should be. Since the supply curve is uncertain in practice, it is difficult to provide guidance on how much to raise or lower the ceiling price in any given case.

A1.4.4 Policy implications

In common with the considerations made earlier regarding the setting of a single ceiling price across provinces and territories, the most desirable approach for setting a single ceiling price across indications depends upon the policy intent.

Note that it is not the role of the Working Group to specify the policy intent. While the implications of some potential policy objectives are considered below, this should not be construed as an endorsement by the Working Group of any particular policy objective. Also note that this analysis is not exhaustive: there are other potential policy objectives and approaches for setting a ceiling price across indications.

Potential policy objective 1

If the policy maker desires that new medicines *do not diminish population health across Canada as a whole*, such that overall consumer surplus is at least zero, then the first approach considered above is inconsistent with this policy objective. This is because this approach results in diminished population health (negative consumer surplus) in all indications except that which is the most cost-effective (in which consumer surplus is zero), resulting in diminished population health (negative consumer surplus) overall.

The second approach comfortably satisfies this policy objective (since it results in positive overall consumer surplus), while the third approach only just satisfies this policy objective (since it results in an overall consumer surplus of zero). The fourth approach *might* satisfy this policy objective if manufacturers are not strategic, but if manufacturers behave strategically then the *expectation* would be that consumer surplus is negative overall, in which case this approach would not satisfy this objective.

It follows that the ceiling price that arises under the third approach (P_{13} in Figure 9D) is the maximum ceiling price that would be consistent with this policy objective. At this ceiling price, overall consumer surplus is zero, analogous to the consumer surplus arising in a standard model of a monopoly with perfect price discrimination.

Potential policy objective 2

If the policy maker instead desires that new medicines *do not diminish population health within any specific indication*, then both the first and third approaches are inconsistent with this policy objective. This is because both approaches result in diminished population health (negative consumer surplus) in at least one indication. Unless manufacturers consistently launch in the least-effective indication first, the fourth approach is also inconsistent with this objective.

The second approach would only just satisfy this policy objective, since consumer surplus is zero in the least cost-effective indication.

It follows that the ceiling price that arises under the second approach (P_{12} in Figure 9C) is the maximum ceiling price that is consistent with this policy objective.

Potential policy objective 3

If the policy maker wishes to set ceiling prices for new medicines so as to *maximize population health across Canada as a whole*, then (in common with the earlier consideration of this policy objective when pricing across provinces and territories) consideration should be given to the location of the supply curve.

As before, a key assumption is that a medicine will not be launched if producer surplus is negative. If a medicine is not launched, the pharmacoeconomic value is zero since there is no resulting net gain in QALYs. For the pharmacoeconomic value to be positive, the medicine must be launched at a ceiling price that results in positive consumer surplus.

Also as before, the most desirable ceiling price under this policy objective is the lowest ceiling price at which producer surplus is non-zero. Depending upon the location of the supply curve, this might be at a ceiling price below P_{12} in Figure 9D, leading to greater consumer surplus than that resulting from any of the four approaches considered above. However, as before, lowering the ceiling price to extract additional consumer surplus carries a risk that producer surplus may become negative, such that the medicine is not launched and consumer surplus is zero.

The highest ceiling price that should be considered under this objective is that which arises under the third approach, P_{13} in Figure 9D, since consumer surplus is zero at this ceiling price (analogous to a standard model of a monopoly with perfect price discrimination).

A1.5 Uncertainty

This framework has so far assumed that ΔH , ΔC and k are known with certainty, such that a demand curve can be plotted at a fixed ceiling price within each province/territory and indication.

In practice, the estimates of ΔH and ΔC arising from probabilistic analyses conducted by CADTH and INESSS are uncertain, and hence the ICER of the new medicine is uncertain. Furthermore, since k is subject to empirical estimation, this will also be uncertain.

A1.5.1 Implications for the demand curve

Since both the ICER and k are uncertain, the ceiling price at which the ICER is equal to k , and hence the location of the demand curve, is also uncertain.

Nevertheless, since CADTH now mandates the use of probabilistic analysis, the analysis output may be used to assign probability distributions to ΔH and ΔC . Similarly, empirical work should allow for a probability distribution to be assigned to k (see, for example, Claxton *et al.* 2015).¹⁰ It follows that it should be possible to assign a probability distribution to the demand curve.

Figure 11 reproduces the demand curve from Figure 1 with a 95% credible interval. In this example, given uncertainty in ΔH , ΔC and k , the net health benefit (consumer surplus) of the medicine is *expected* to be zero at a ceiling price of P_1 (illustrated by the 'mean' demand curve). Given this uncertainty, there is a 95% probability that the net health benefit is *actually* zero at a ceiling price between P_{14} and P_{15} (illustrated by the 'U 95%' and 'L 95%' demand curves).

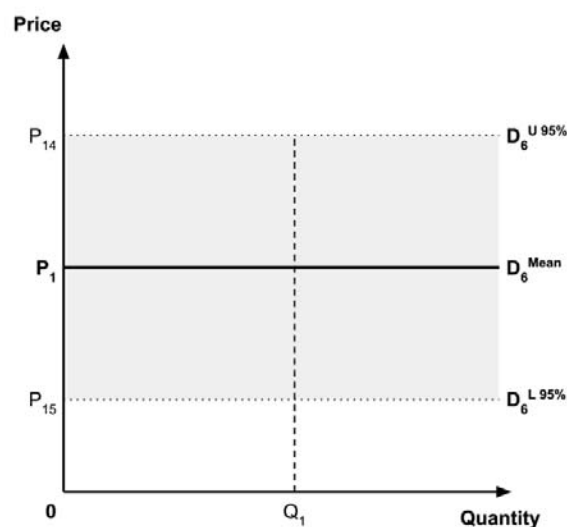


Figure 11: Demand curve subject to a 95% credible interval

A1.5.2 Expected loss in economic surplus

Since the ceiling price at which the net health benefit (consumer surplus) of the medicine is *actually* zero is uncertain, there is a possibility that the ceiling price at which a new medicine is *expected* to provide zero consumer surplus (P_1 in Figure 11) will *actually* result in positive consumer surplus, and similarly there is a possibility that this ceiling price will *actually* result in negative consumer surplus. There is also a possibility that this ceiling price will *actually* result in zero consumer surplus, which would arise if P_1 lies below the supply curve (such that the medicine is not launched).

Consider Figure 12A. In this example, the *actual* ceiling price at which net health benefit (consumer surplus) is zero is P_{16} . This is the ceiling price at which the demand curve would be plotted if ΔH , ΔC and k were known with certainty. Since these parameters are uncertain, the true location of this *actual* demand curve is unknown (and is plotted with a dashed line). Instead, we have an estimate of the *expected* ceiling price at which net health benefit is zero (P_1), and also an estimate of the 95% credible interval (between P_{14} and P_{15}).

Suppose the PMPRB specifies a ceiling price of P_1 , based on the *expected* (mean) demand curve. Because P_1 is lower than the (unknown) *actual* demand curve, but above the (unknown) supply curve at quantity Q^1 , it follows that a ceiling price of P_1 will result in a positive consumer surplus (illustrated by the combined area of regions 34, 35 and 36). Producer surplus will also be positive (illustrated by the combined area of regions 37 and 38, minus the combined area of regions 33 and 34), but lower than it would have been if the ceiling price were set according to the *actual* demand curve (with the reduction in producer surplus equal to the gain in consumer surplus). Critically, because producer surplus is positive at P_1 , the medicine is still launched. It follows that, *in this example*, uncertainty has resulted in a *positive* consumer surplus.

Now consider Figure 12B. In this example, the *actual* demand curve (P_{17}) lies *below* the expected (mean) demand curve (P_1). It follows that, if the medicine is adopted at a ceiling price P_1 , then consumer surplus will be *negative* (illustrated by the combined area of regions 40, 41 and 42), since a higher ceiling price is paid than that at which consumer surplus is zero. Producer surplus is greater than it would have been in the absence of uncertainty (illustrated by the combined area of regions 41 to 44, minus the area of region 39), with this gain in producer surplus equal to the reduction in consumer surplus (illustrated by the combined area of regions 40, 41 and 42).

This brings us to a key result. Provided that the medicine is launched at a ceiling price coinciding with the *expected* demand curve (a crucial requirement considered further below), the *expected* consumer surplus is zero (analogous with a model of a monopoly with perfect price discrimination). The *actual* consumer surplus may be positive (as in Figure 12A) or negative (as in Figure 12B), but the *expected* consumer surplus is zero.

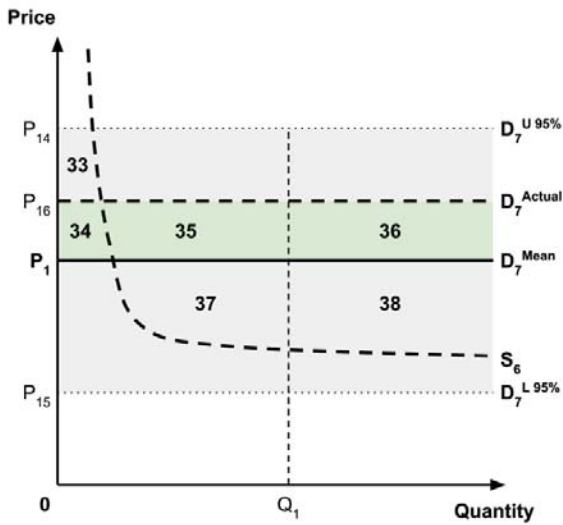


Figure 12A: Example where the actual demand curve (P_{16}) lies *above* the expected demand curve (P_1) and the medicine is launched

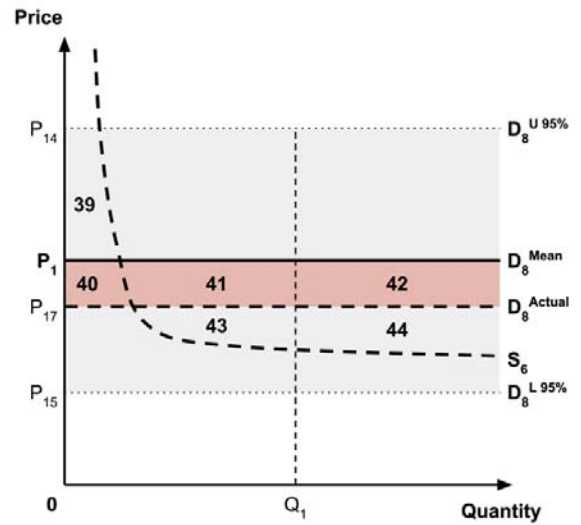


Figure 12B: Example where the actual demand curve (P_{17}) lies *below* the expected demand curve (P_1) and the medicine is launched

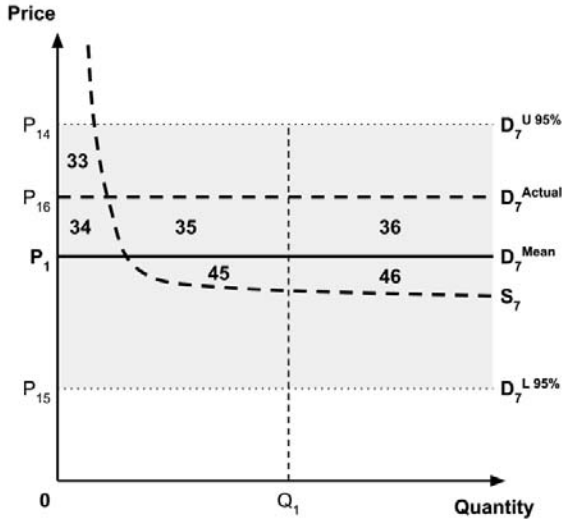


Figure 12C: Example where the actual demand curve (P_{16}) lies *above* the expected demand curve (P_1) and the medicine is *not* launched

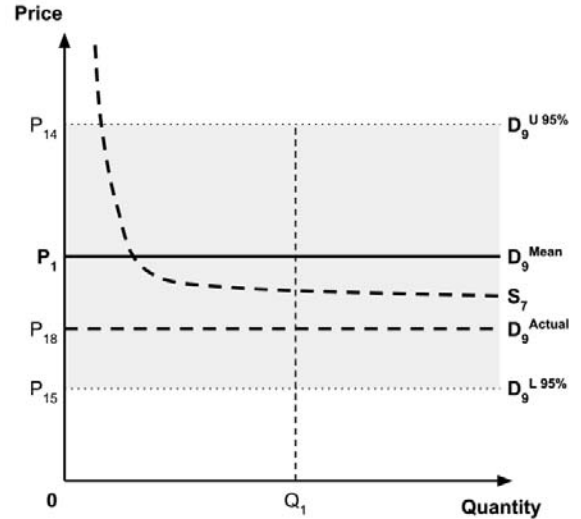


Figure 12D: Example where the actual demand curve (P_{18}) lies *below* the expected demand curve (P_1) and the medicine is *not* launched

However, this result does not hold if the medicine is *not launched* as a result of uncertainty.

Consider Figure 12C. In this example, the *actual* and *expected* demand curves are identical to those in Figure 12A, but the supply curve is now higher (S_7). If the ceiling price coinciding with the *actual* demand curve (P_{16}) were known in practice and offered to the manufacturer, then the medicine would be launched since the producer surplus would be positive (illustrated by the combined area of regions 35, 36, 45 and 46, minus the area of region 33). However, this is not possible because the *actual* demand curve is unknown. If the manufacturer is instead offered the ceiling price coinciding with the *expected* demand curve (P_1), then the manufacturer will choose *not* to launch the medicine, because the producer surplus would now be negative (illustrated by the combined area of regions 45 and 46, minus the combined area of regions 33 and 34). Since the producer surplus would be negative, and so the medicine is not launched, it follows that both the consumer surplus and producer surplus are zero. Compared to Figure 12A, in which both consumer and producer surplus were positive since the medicine still launched, in this example the uncertainty results in a loss of economic surplus (with the total loss illustrated by the combined area of regions 35, 36, 45 and 46, minus the area of region 33).

Finally, consider Figure 12D. The *expected* demand curve and supply curve are identical to those in Figure 12C, so again the medicine is *not* launched because it would have negative producer surplus. However, in this example the *actual* demand curve (P_{18}) is lower than the *expected* demand curve (P_1). As a result, the medicine would not have launched anyway in the absence of uncertainty, such that the uncertainty does *not* result in a loss in economic surplus (since there would have been none anyway).

To summarize the results from the examples above:

1. If the medicine is launched at a ceiling price coinciding with the *expected* demand curve then the *expected* consumer and producer surplus is zero.
2. If the medicine is unprofitable at a ceiling price coinciding with the *expected* demand curve, and is *also* unprofitable at a ceiling price coinciding with the *actual* demand curve, then the consumer surplus is zero.
3. If the medicine is unprofitable at a ceiling price coinciding with the *expected* demand curve, but would have been profitable at a ceiling price coinciding with the *actual* demand curve, then the impact of uncertainty is to *diminish* the total economic surplus such that *expected* consumer surplus at a ceiling price coinciding with the expected demand curve is *negative*.

It follows from this third result that uncertainty is associated with an expected loss in consumer surplus, such that reducing uncertainty results in an expected gain in consumer surplus.

A1.6 Market size

The PMPRB has proposed that a ‘market size adjustment’ may be applied to the ceiling price for some Category 1 medicines. This includes a potential upwards ceiling price adjustment for medicines with small market size and, independently, a potential downwards ceiling price adjustment for medicines with large market size.

The first of these would have the effect of increasing the producer surplus (at the expense of consumer surplus) for medicines with small market size. The second would increase the consumer surplus (at the expense of producer surplus) for medicines with large market size.

Consider Figure 13A, which reproduces the demand and supply curves for a hypothetical new medicine from Figure 4A.

For simplicity, it is assumed that the medicine has a single indication and there are no differences in k across provinces and territories, such that there is a single horizontal demand curve (D_1) at a ceiling price of P_1 . It is also assumed that the ceiling price of the medicine is P_1 , such that consumer surplus is zero (in the absence of a market size adjustment).

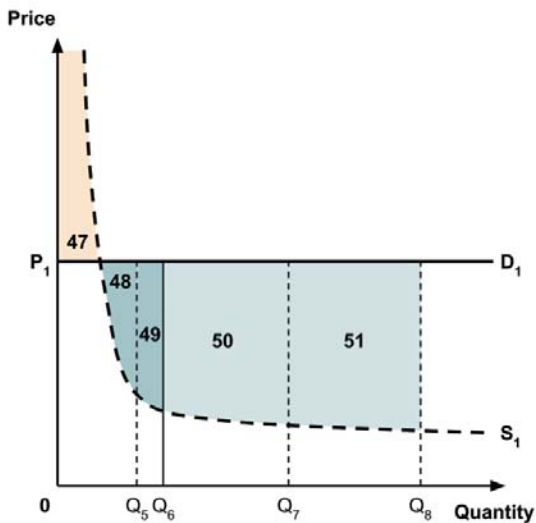


Figure 13A: Without any ‘market size adjustment’

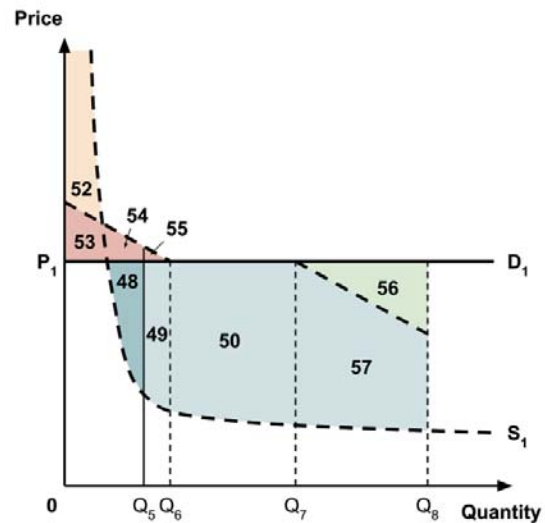


Figure 13B: With a hypothetical ‘market size adjustment’

If this medicine has very small market size (quantity Q_5), then it will have negative producer surplus (as illustrated by the area of region 48 minus the area of region 47), such that it would not be profitable to launch. If the medicine has slightly larger market size (Q_6), then the producer surplus increases (by the area of region 49) but is now zero, such that the manufacturer is ambivalent about launching the medicine. With even larger market size (Q_7), the producer surplus increases further (by the area of region 50), such that the medicine is now profitable. And with the largest market size (Q_8), the medicine has an even greater producer surplus (as illustrated by the combined area of regions 48, 49, 50 and 51, minus the area of region 47).

Note that Q_6 is the minimum market size at which the medicine is profitable. A smaller market size results in negative producer surplus, while a larger market size results in increasingly positive producer surplus.

A1.6.1 Implications of a market size adjustment

Now consider Figure 13B, which illustrates a hypothetical 'market size adjustment'. Following this market size adjustment, medicines with market size below Q_6 receive a higher ceiling price, while medicines with market size above Q_7 receive a lower ceiling price.

In order to allow for comparisons between medicines with small and large market size, it will now be assumed that there are many new medicines, each with identical demand and supply curves as plotted in Figure 13B, with these medicines differing in terms of their market size.

This hypothetical market size adjustment has a number of implications.

Implication 1: Increased consumer surplus from medicines with large market size

The reduction in the ceiling price for medicines with large market size results in an increase in consumer surplus (as illustrated by the area of region 56 for a medicine with market size Q_8).

Producer surplus for medicines with large market size is reduced by an equivalent amount, but remains positive because it was sufficiently large prior to the reduction in ceiling price.

Since the market size adjustment did not cause the demand curve to cross the supply curve, the producer surplus for a medicine with market size Q_8 remains larger than the producer surplus at any smaller market size (as illustrated by the combined area of regions 48, 49, 50 and 57, minus the combined area of regions 52 and 53).

Implication 2: Reduced consumer surplus from medicines with small market size

A higher ceiling price for medicines with small market size results in greater producer surplus (as illustrated by the combined area of regions 53, 54 and 55), but a correspondingly lower consumer surplus.

Since (in this example) consumer surplus was zero prior to the market size adjustment, it follows that consumer surplus is now negative for medicines with small market size.

Implication 3: Increased profitability for medicines with small market size

For a medicine with a market size of Q_5 , the producer surplus following the market size adjustment is zero (as illustrated by the area of regions 48, 53 and 54, minus the area of region 52), where previously it was negative.

For a medicine with a market size of Q_6 , the producer surplus is now positive (as illustrated by the combined area of regions 48, 49, 53, 54 and 55, minus the area of region 52), where previously it was zero.

It follows that the minimum market size at which a medicine is profitable has fallen from Q_6 (prior to the market size adjustment) to Q_7 . Medicines with a market size between Q_5 and Q_6 , which were unprofitable prior to the market size adjustment, now have positive producer surplus. This might, in turn, result in greater access to medicines with small market size.

Appendix 2: Materials Presented at Meetings of the Working Group

Appendix 2.1: Slides from 26 July 2018 (Dr Mike Paulden)

Working Group to Inform the Patented Medicine Prices Review Board (PMPRB) Steering Committee on Modernization of Price Review Process Guidelines

Alt Hotel, Ottawa, ON
26 July 2018

Chair: Dr Mike Paulden

Background

The Patented Medicine Prices Review Board (PMPRB) recently established a 'Steering Committee on Modernization of Price Review Process Guidelines'.

The mandate of this Steering Committee is to assist the PMPRB in synthesizing stakeholder views on key technical and operational modalities of the PMPRB's new draft Guidelines.

The Steering Committee's work will be based in part on the analysis and recommendations of a technical Working Group, which will examine certain issues that the Steering Committee believes would benefit from the review of experts in health technology assessment and other economic and scientific matters.

Background

The Working Group will comprise leading experts in pharmacoeconomics and the clinical evaluation of pharmaceuticals.

The Working Group will meet four times between July and October 2018: twice in-person in Ottawa, and twice via video-conference.

A report of the Working Group's deliberations and recommendations will be produced by the chair and submitted to the Steering Committee for consideration in October 2018.

Members

- 1. Dr Chris Cameron (Dalhousie University and Cornerstone Research Group);*
- 2. Dr Tammy Clifford (University of Ottawa and CADTH);*
- 3. Dr Doug Coyle (University of Ottawa);*
- 4. Patrick Duford (INESSS);*
- 5. Don Husereau (Institute of Health Economics);*
- 6. Dr Peter Jamieson (University of Calgary);*
- 7. Dr Frédérick Lavoie (Pfizer Canada);*
- 8. Dr Karen Lee (University of Ottawa and CADTH);*
- 9. Dr Christopher McCabe (University of Alberta and Institute of Health Economics);*
- 10. Dr Stuart Peacock (Simon Fraser University and BC Cancer Agency);*
- 11. Maureen Smith (Patient – Health Quality Ontario);*
- 12. Geoff Sprang (Agmen);*
- 13. Dr Tania Stafinski (University of Alberta).*

Observers and Reviewers

Observers

1. *Edward Burrows (Innovation, Science and Economic Development);*
2. *Nelson Millar (Health Canada).*

External reviewer

1. *Dr Mark Sculpher (University of York).*

Confidentiality

Working Group members may consult with non-members on an ongoing basis but are expected to maintain the confidentiality of any materials provided to them during the course of their work.

The names of the members of the Working Group will be published on the PMPRB's website, along with a report of its deliberations, analysis and recommendations.

Governance and procedure

It is recognized that members of the Working Group may hold opposing points of view on the above issues and/or disagree with the policy rationale underlying the changes to the PMPRB's Guidelines.

Members are nonetheless encouraged to work together constructively to assist the Working Group in carrying out its function.

Governance and procedure

The chair is expected to foster consensus among members, but in order to ensure that Working Group deliberations are as focused and productive as possible, the chair shall have final say on all matters of governance and procedure.

Members who disagree with a decision of the chair in this regard can request that their objection be noted on the record.

The chair shall make every effort to ensure that the Working Group's final report accurately reflects any important points of convergence or contention between members.

Schedule

Date	Event	Purpose
26 July 2018	Full day in-person meeting in Ottawa	Overview of Working Group objectives. Summary of specific areas of focus under consideration. Allocation of tasks among Working Group members.
Week of 20 August 2018 (TBC)	Two hour video-conference	Update on Working Group status. Opportunity for input from Working Group members.
Week of 10 September 2018 (TBC)	Two hour video-conference	Update on Working Group status. Opportunity for input from Working Group members.
5 October 2018	Draft report submitted to PMPRB	Opportunity for input from PMPRB and Working Group members.
12 October 2018	Full day in-person meeting in Ottawa	Present draft report. Report draft recommendations. Final opportunity for input from PMPRB and Working Group members.
26 October 2018	Final report delivered to PMPRB	Final deliverable to PMPRB.

Deliverables

A draft report will be circulated to the Steering Committee and Working Group members on 5 October 2018, prior to the final in-person meeting in Ottawa.

Following delivery of the final report, the chair will be willing to present the recommendations of the Working Group to stakeholders and other interested parties, subject to availability.

Background and
Overview

Group discussion

Areas of focus

1. Options for determining what drugs fall into 'Category 1'
2. Application of supply-side cost effectiveness thresholds in setting ceiling prices for Category 1 drugs
3. Drugs with multiple indications
4. Options for using the CADTH and/or INESS reference case analyses to set a ceiling price
5. Perspectives
6. Application of the market size factor in setting ceiling prices

1. Options for determining what drugs fall into 'Category 1'

A Category 1 drug is one for which a preliminary review of the available clinical, pharmacoeconomic, market impact, treatment cost and other relevant data would suggest is at elevated risk of excessive pricing.

The following criteria have been identified as supporting a Category 1 classification:

- a) The drug is 'first in class' or a 'substantial' improvement over existing options*
- b) The drug's opportunity cost exceeds its expected health gain*
- c) The drug is expected to have a high market impact*
- d) The drug has a high average annual treatment cost*

Should other criteria be considered?

What are the relevant metrics for selecting drugs that meet the identified criteria and what options exist for using these metrics?

2. Application of supply-side cost effectiveness thresholds in setting ceiling prices for Category 1 drugs

Potential approaches for implementing a price ceiling based on a drug's opportunity cost.

Potential approaches for allowing price ceilings above opportunity cost based on a higher willingness to pay for certain types of drugs (e.g. pediatric, rare, oncology, etc)

What are the potential approaches for considering a drug's opportunity cost and implementing a price ceiling?

Should higher price ceiling(s) be adopted for certain types of drugs? If so, which drugs? How should the higher price ceiling(s) be determined?

3. Drugs with multiple indications

Options for addressing drugs with multiple indications (e.g. multiple price ceilings or a single ceiling reflecting one particular indication).

What are the available options regarding pricing for multiple indications?

Which option should be recommended, and why?

4. Accounting for uncertainty

Options for using the CADTH and/or INESS reference case analyses to set a ceiling price.

Options for accounting for and/or addressing uncertainty in the point estimate for each value-based price ceiling.

Do existing ‘reference case’ analyses provide the most appropriate estimates from which to derive a ceiling price?

If not, what modifications from the ‘reference case’ assumptions are desirable?

How should uncertainty be accounted for, or addressed, when setting price ceilings?

5. Perspectives

Options to account for the consideration of a public health care system vs societal perspective, including the option of applying a higher value-based price ceiling in cases where there is a ‘significant’ difference between price ceilings under each perspective.

How to define a ‘significant’ difference in price ceilings between each perspective.

What are the key differences between a public health care system vs societal perspective?

What are the options to account for these differences?

How should a ‘significant’ difference be defined?

6. Application of the market size factor in setting ceiling prices

Approaches to derive an appropriate affordability adjustment to a drug's ceiling price based on an application of the market size and GDP factors (e.g. based on the US 'ICER' approach).

What approaches are available to consider an 'affordability adjustment' to a drug's ceiling price?

Should other factors be considered (in addition to market size and GDP)?

How should each of these factors be considered?

Closing

Appendix 2.2: Note on Uncertainty (Dr Christopher McCabe)

Considering uncertainty when setting a ceiling price for technologies using a cost effectiveness threshold: a note to the PMPRB Technical Working Group.

Christopher McCabe PhD,
Professor of Health Economics, Faculty of Medicine and Dentistry,
University of Alberta

CEO and Executive Director, Institute of Health Economics, Alberta

Background

The Patented Medicines Price Review Board (PMPRB) are considering using a cost effectiveness threshold to identify a ceiling price for new patented medicines in Canada [hereafter referred to as Value Based Pricing Ceiling (VBPC)]. As part of the process for revising its review process, PMPRB has established a technical working group to comment on technical/methods issues relating to this proposal, that have been identified in the consultation process. One of the technical issues that PMPRB are seeking commentary on is the mechanisms for dealing with uncertainty in the evidence base, within analyses undertaken for VBPC. In this note, we describe the nature of the uncertainties in the evidence base and how they may be addressed analytically within the standard framework of cost effectiveness analysis, in a timely manner from the perspective of the PMPRB's objective of providing timely access to innovation.

The contents of this note should not be interpreted as providing any comment on the desirability or otherwise of VBPC in Canada. Further, the contents of this note should not be interpreted as representing the views of the Institute of Health Economics, its Board, Members or funders, on any of the issues relating to VBPC in Canada.

The remainder of this note is structured as follows: first we describe the categories of uncertainty that a VBPC process *could* consider, the constituent components of those categories and how they relate to the decision that a VBPC setting body such as PMPRB is charged with making; then we rehearse key concepts from decision science: decision uncertainty, the expected cost of making the wrong decision, value of information, and the associated concept of expected net benefit of sampling; finally we describe how these concepts could be used by PMPRB to identify a VBPC. We end with a short note on why the PMPRB (or any VBPC authority) should not be considering uncertainty in the Incremental Cost Effectiveness Ratio for a specific product in setting a ceiling price.

Categories of uncertainty potentially pertinent to VBPC process

There are two models of the cost effectiveness threshold; often referred to as the Demand side and Supply side Threshold respectively. The Demand side threshold can usefully be differentiated from the supply side threshold by labelling it the Willingness to Pay for Health. (ref) The Supply side threshold represents the value of the health displaced by the adoption of a new technology under a fixed and fully allocated health system budget. This is often referred to as the Opportunity Cost of adopting a new technology – even though this is not a technically correct use of the term Opportunity Cost. (ref). Both forms of the cost effectiveness threshold are empirical quantities, which in principle can be measured with a degree of uncertainty. For the purposes of this note, it does not matter whether the VBPC is established with reference to a Demand or Supply side threshold.

If we only know the cost effectiveness threshold with uncertainty, there is a risk that the empirical value will be higher or lower than the true value. The econometric studies that typically provide empirical estimates produce an expected value and a description of the uncertainty around that expected value via Standard Errors. These data can be used to characterise a probability distribution that describes the range of credible values for the threshold and the probability that any specific value in the credible range is the true value. This

information allows analysts to examine two important questions: (1) What is the probability that that using the estimate of the cost effectiveness threshold to set a ceiling price, we introduce a technology to the market that will displace more health than it produces, because the estimated threshold is higher than the actual threshold (Type 1 Error); and (2) What is the probability that that using the estimate of the cost effectiveness threshold to set a ceiling price, we exclude a technology from the market that would produce more health than it displaces, because the estimated threshold is lower than the actual threshold (Type 2 Error).

In addition to uncertainty regarding the true value of the cost effectiveness threshold, there is uncertainty about the true value (cost effectiveness) of the technologies. Much, although not all, of this uncertainty derives from uncertainty in the evidence base for the new technology, the technologies it is being compared to and the epidemiology and natural history of the condition that the technology targets. In this context, the evidence base includes resource use, costs and quality of life, as well as the more conventional concerns of effectiveness and safety. Uncertainty in the evidence base will contribute to (a) the risk of adopting a technology that should not be adopted because its actual cost effectiveness is above than the threshold even though the estimated cost effectiveness is below the threshold; and (b) rejecting a technology that should be accepted because its estimated cost effectiveness is greater than the threshold even though its actual cost effectiveness is below the threshold. The uncertainty regarding each component of the evidence base can be assessed from the perspective off whether resolving the uncertainty would be expected to change the decision. This is the foundational observation of Value of Information Analysis, a well established set of techniques from decision science. In the next section, we will provide a brief description of the concepts and specific applications of Value of Information Analysis.

Decision making, uncertainty and value of information

Decisions are by definition dichotomous. We choose to do one thing and in doing so, we choose not to do the alternative. Evidence, by contrast, tends to be uncertain and thus sits on a

continuum of probability. Cost effectiveness analysis synthesises all available (and relevant) evidence to estimate the expected incremental costs and incremental effects of the new therapy compared to one or more currently used therapies. Because the evidence is not certain, the estimates of the costs and effects are drawn from distributions, which reflect the uncertainty in the evidence base pertaining to the clinical pathway patients would follow when receiving the alternative therapies, the resource use, costs and health related quality of life associated with the different components of those clinical pathways.

As indicated above, decision making using cost effectiveness analysis requires the specification of a threshold value for the incremental cost effectiveness ratio, above which the new therapy is considered poor value and below which it is considered good value. When the uncertainty in the cost effectiveness is recognised and quantified – as it is in cost effectiveness analyses that comply with good practice guidelines – we can quantify the probability that the decision based upon the expected incremental cost effectiveness ratio will be the wrong decision (either rejecting a good value therapy or accepting a poor value therapy). The probability of making the wrong decision is called the ‘Decision Uncertainty’. Cost effectiveness analysis allows us to go further than simply characterising Decision Uncertainty; it allows us to attach a value to making the wrong decision. If we make the wrong decision, then we will be giving up health – by either adopting a technology that displaces more health elsewhere in the system due to its true excess cost, or by continuing to fund a technology within the health care system that actually produces less health than the new technology would if we adopted it. The cost effectiveness threshold (\$s per Unit of Health gained) can be applied to the health loss associated with making the wrong decision, to quantify if the decision is wrong. The expected cost of making the wrong decision is obtained by weighting this by the probability of making the wrong decision given current evidence.

There are broadly two responses to concern about making a wrong decision given the current evidence. The first is to collect more evidence, which improves the evidence base and thereby reduces the decision uncertainty. The second is to modify to the point where the cost of making

the wrong decision is less than the cost of delaying the decision to allow more evidence to be collected. Both of these approaches can be formalised through the using the Value of Information framework. The easiest way of thinking about the value of information is as the reduction in the expected cost of making the wrong decision attributable the additional information provided research, net the cost of undertaking the research.¹ When we consider the value of the additional information provides by a specific research study and net out the cost of the research, this is referred to as the Net Benefit of Sampling.

Having reviewed these key concepts, we now turn to consider how a VBPC framework could take account of uncertainty in the value of the cost effectiveness threshold.

[Incorporating uncertainty in the value of the cost effectiveness threshold into a VBPC](#)

We start by re-iterating that the cost effectiveness threshold is an empirical quantity that can be estimated with uncertainty, therefore we can characterize the uncertainty and its value using the methods of probabilistic analysis and value of information analysis that are recommended in the Canadian Agency for Drugs and Technologies in Health (CADTH) Guideline for Economic Evaluations: Canada. (2017).

The cost making the wrong decision with regard to uncertainty in the threshold is two-sided - setting a price that is too high because the threshold value is actually lower than the estimate leading to a loss of health; and setting the price too low leading to the technology being withheld from the market, because the actual threshold is higher than the estimate. It follows that the expected value of the wrong decision is the sum of these two factors.

¹ The definition of cost of the research includes any health gains foregone and/or harms incurred whilst the research is undertaken as well as all financial costs associated with the research.

The VBPC setting authority does not know the price that is consistent with a company's minimum willingness to accept. Given the consistent messages from all levels of government that the policy objective prioritises access to new therapies, it is appropriate for the analyst to adopt a risk averse position and assume that company's minimum willingness to pay requires only a marginal increase in the cost effectiveness threshold and thereby maximize the probability that we have incorrectly excluded them. Hence the probability of making a Type 1 error is the portion of the distribution of the threshold parameters that is above the expected value. The cost of a Type 1 error is the sum of the net benefit calculated using the range of threshold values above the expected value weighted by the probability that each value is the true value multiplied by the population that would benefit.

The cost of a Type 2 error due to threshold uncertainty is slightly different because the technology is provided but it is possible that the ceiling price is over-rewarding it. Therefore, the cost of making the wrong decision is the sum of the *difference* between the net benefit estimated using the expected threshold and each possible threshold value below the expected value, weighted by the probability that it is the actual value. This is then multiplied by the size of the patient population to get the total cost.

If the sum of the cost of these two types of error is not equal to zero, and there is no reason a priori why it should be, then the threshold should be increased or decreased to identify the value which minimizes the sum of the two effects. Theoretically, when the minimum loss identified by this process is non-zero, consideration should be given to the question of whether the cost of further research to reduce the uncertainty in the true value of the threshold is greater than the value of the uncertainty. Pragmatically this would likely not be practical, as this would be a technology specific assessment, and the desirability of consistent and timely VBPC decisions would indicate argue against such an approach. However, period reviews of the total loss attributable to uncertainty in the value of threshold across a portfolio of assessments, would provide empirical evidence on the value of further research to improve the evidence on

the cost effectiveness threshold used.

Uncertainty in the Incremental Cost Effectiveness Ratio and VBPC

It is worth noting that there is uncertainty in the value of the technology, that this uncertainty is empirical and hence in principle can be addressed using the same concepts as outlined above. We would also note that if such an approach is adopted it should focus only on the components of the evidence base that the company could realistically influence through the design of the Research and Development programme that brought the product to market – broadly safety, effectiveness, resource utilisation and health related quality of life.

However, in the context of a VBPC framework, we argue that value of the uncertainty in the evidence base for the technology can be considered out of scope. We hold this position for two reasons. First, the function of the VBPC authority is to set a maximum price consistent with access to the market. In the form described above, we have set a specific risk attitude – averse to Type 1 errors – and this risk attitude may not be the one that health care payers wish to adopt. Health care payers have considerable experience of addressing uncertainty in the evidence base for a technology and understand their attitude to such risk and their preferred strategies for managing it. It is not obvious that there is value in the VBPC authority acting in the space.

Secondly, increasingly innovative technologies are receiving conditional licensing approval; i.e. the regulator provides temporary market access in order to allow research that will reduce the uncertainty in the evidence base for their value. If this same uncertainty were considered by the VBPC authority, this would drive down the price of the technology and reduce the likelihood that the technology would enter this market. The policies of the licensing and VBPC authorities would be in direct conflict.

3rd October 2018

Appendix 2.3: Slides from 12 October 2018 (Dr Mike Paulden)

Strategic Behaviour and the Cost-Effectiveness Threshold



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1

Supply-side threshold (k)

Determined by the opportunity cost of new interventions



2

1

Demand-side threshold (v)

Determined by society's willingness-to-pay for improved health 'benefit'



3

Additional considerations

- In practice, funding decisions involve a number of **complex considerations** which are *not* reflected by **conventional demand/supply-side thresholds**
- Funding might **displace health care services** that provide 'benefit' to other patients - *not accounted for in a demand-side approach*
- Specifying λ might result in **strategic pricing behaviour** from manufacturers
- Manufacturers may be **unwilling to supply new technologies** if λ is **low**, but may make **large profits** at the expense of **population health** if λ is **high**
- A decision maker interested in both **consumer** and **producer** interests may wish to understand the **trade-offs** associated with **different values of λ**

4

A new conceptual model

5

Overview

- This paper proposes a **new conceptual model of the cost-effectiveness threshold** that incorporates these **additional considerations**
- Considers both **opportunity cost** and society's **willingness-to-pay** for health 'benefit' from conventional **supply-side** and **demand-side** approaches
- Considers **costs incurred by manufacturers** in developing technologies and the **incentive for manufacturers to strategically price up to λ**
- Allows for considerations of '**consumer surplus**' and '**producer surplus**', so decision makers may consider **how λ impacts upon the distribution of surplus between consumers (patients) and producers (manufacturers)**

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Slide 6

6

Assumptions

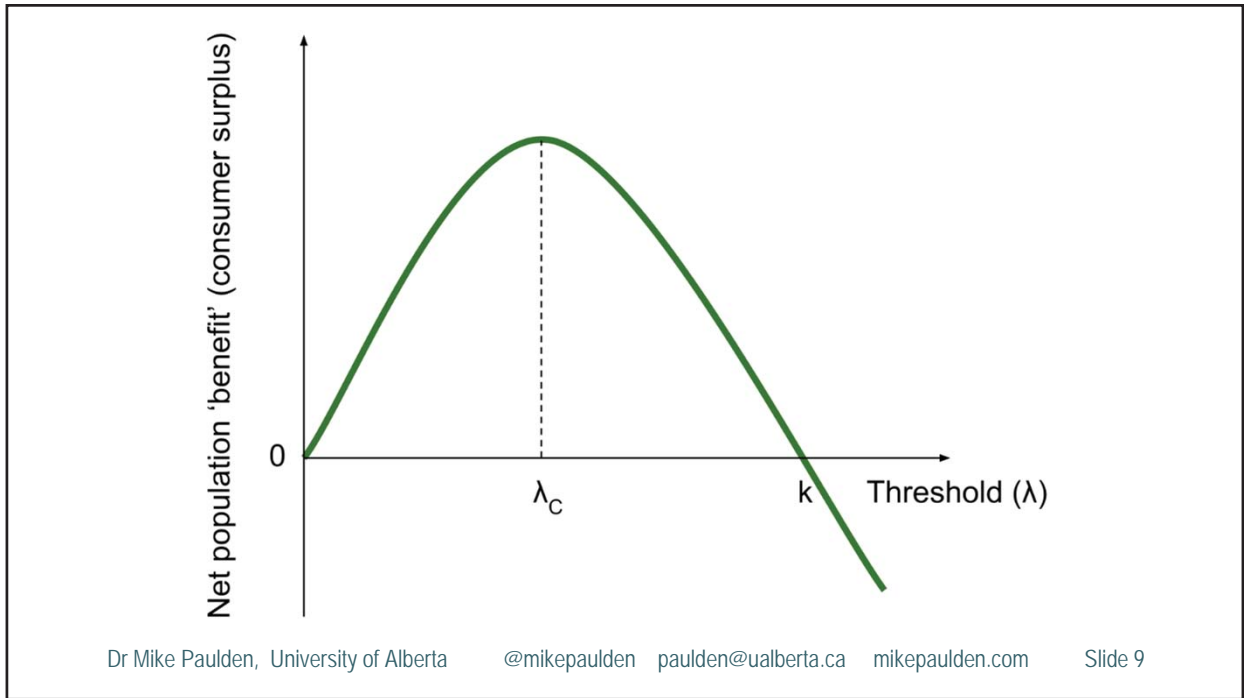
1. There is an accepted measure of **'benefit'** that patients derive from health care
2. **Funding new technologies** has an **opportunity cost** in terms of **foregone 'benefit'**
3. New technologies are **costly** to produce, and manufacturers will **not supply at a loss**
4. A **single threshold**, λ , is **publicly specified** by a health care system decision maker, with **new technologies adopted only if the ICER is less than λ**
5. Manufacturers of new technologies are **protected from price competition** (e.g. through the **patent system**), allowing for **super-normal profits**
6. Each adopted new technology is **strategically priced** such that the **ICER is equal to λ**
7. **Distributions** of **'reserve prices'** and **'reserve ICERs'** are **broad and continuous**
8. All 'reserve ICERs' are **non-negative** (technologies do not 'dominate' at 'reserve price')
9. Each new technology is **independent** and **developed by a different manufacturer**

Dr Mike Paulden, University of Alberta @mikepaulden paulden@ualberta.ca mikepaulden.com Slide 7

7

Consumer perspective

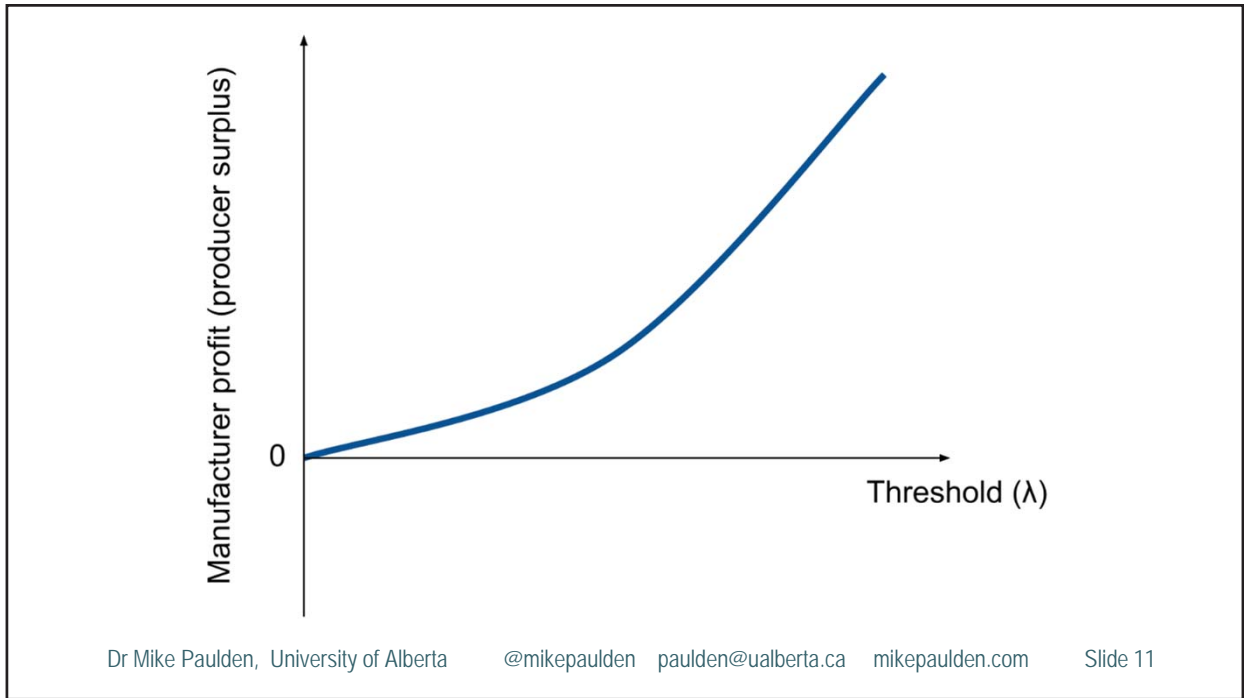
8



9

Producer perspective

10



11

Combining the perspectives

12

Converting into a common metric

- Unless the measure of 'benefit' considered under the consumer perspective is already specified in **monetary terms**, combining consumer and producer surplus requires that each be considered using a **common metric**
- Whether this is done by converting consumer surplus into monetary terms or by converting producer surplus into units of 'benefit' is immaterial; the challenge is **identifying an appropriate conversion rate**
- A conventional **demand-side threshold** provides a natural source for such a conversion rate, since it provides an estimate of the **monetary value of a unit of 'benefit'** that **reflects society's preferences** (denoted as v)

Dr Mike Paulden, University of Alberta

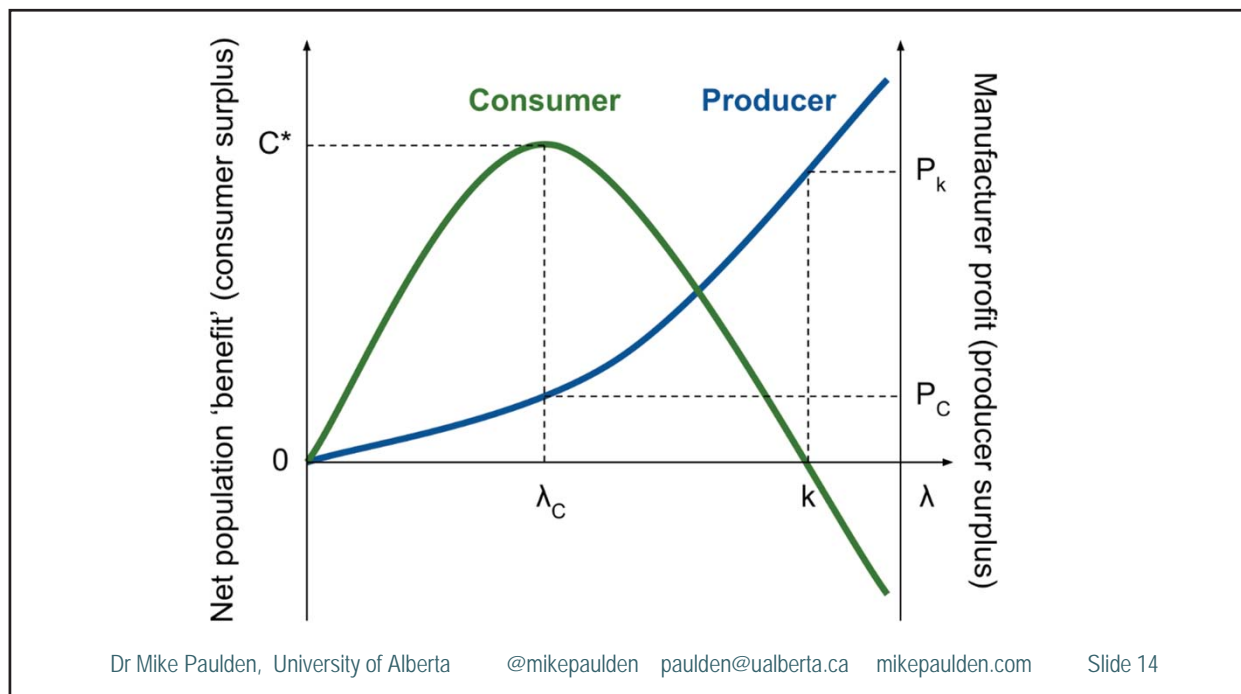
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Slide 13

13



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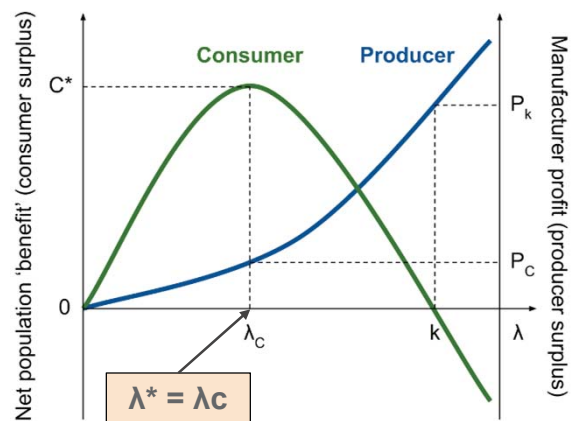
Slide 14

14

Policy objectives

15

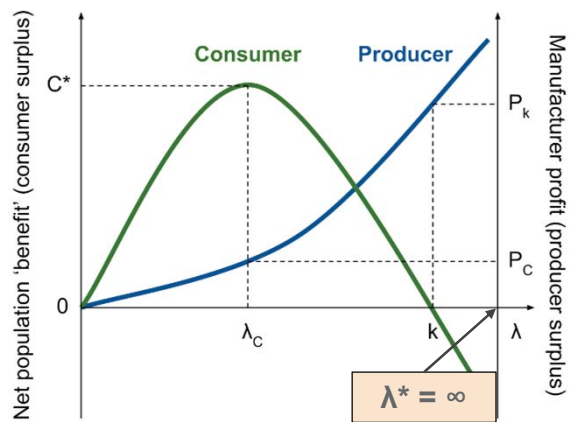
'Maximize
consumer
surplus'



Consumer surplus is maximized by
specifying a threshold of λ_c .

16

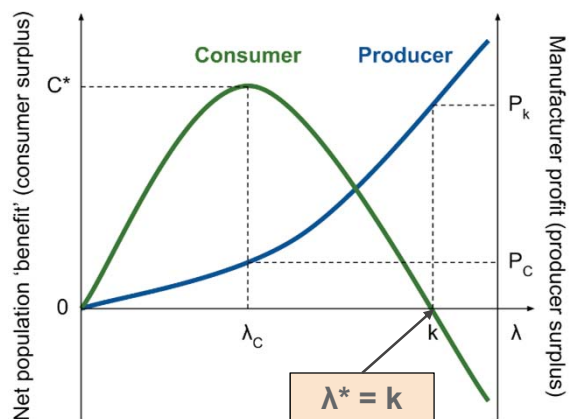
'Maximize producer surplus'



Producer surplus is maximized with an **infinitely high threshold**.

17

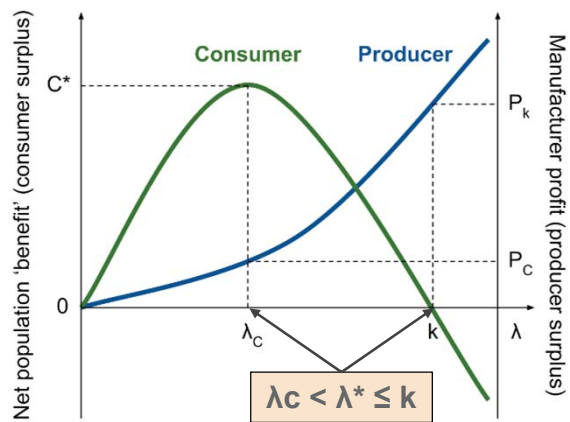
'Max producer surplus, subject to consumer and producer surplus each being non-negative'



Since producer surplus increases with the threshold, and consumer surplus is negative at any threshold above k , this objective is satisfied by specifying a threshold of k .

18

'Maximize the combined surplus, subject to each being non-negative'



Since consumer and producer surplus both increase with the threshold up to λ_c , but consumer surplus is negative above k , the optimal threshold must lie between λ_c and k .

19

Conclusions

20

Implications for policy, theory, and empirical research

- The **optimal threshold** depends critically upon the **policy objective**
- Depending on the objective, the optimal threshold may be **lower or higher** than **either conventional approach** (supply-side or demand-side)
- A **supply-side** estimate of the threshold (k) is necessary to understand the shape of the **consumer threshold curve** and the **optimal threshold 'range'**
- A **demand-side** estimate of the threshold (v) is necessary to **convert consumer and producer surplus into a common metric**
- Future **empirical research** must estimate **not only k and v** , but also the **shapes of the consumer and producer threshold curves**

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Slide 21

21

Download slides from
<https://goo.gl/Mv66HD>
or by scanning barcode



Any questions?

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Slide 22

22

Appendix 2.4: Slides from 12 October 2018 (Dr Christopher McCabe)

Supply side cost effectiveness thresholds for setting a ceiling price: some tools for unpacking the issues

Christopher McCabe PhD
University of Alberta
&
Institute of Health Economics

1

Decision problem

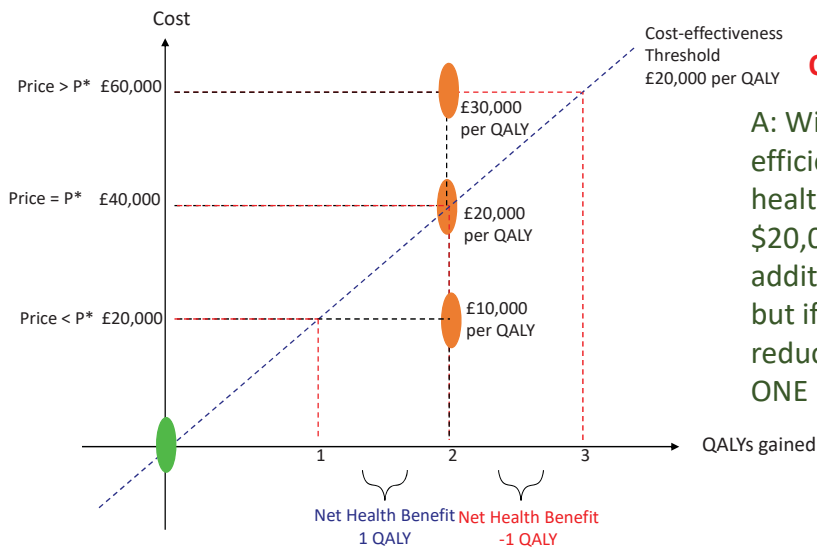
A new drug has been licensed that is expected to improve the health of recipients by two Quality Adjusted Life Years compared to current best practice.

What should the price regulator consider in arriving at a maximum price for this new drug?

1. Expected impact on population health
2. Expected impact on health system sustainability
3. Expected value of health = $f(H.(d,p,t))$
4. Reward to innovation = premium over cost of production of the innovation
5. Access to innovative treatments
6. Uncertainty

2

Expected impact on health system sustainability

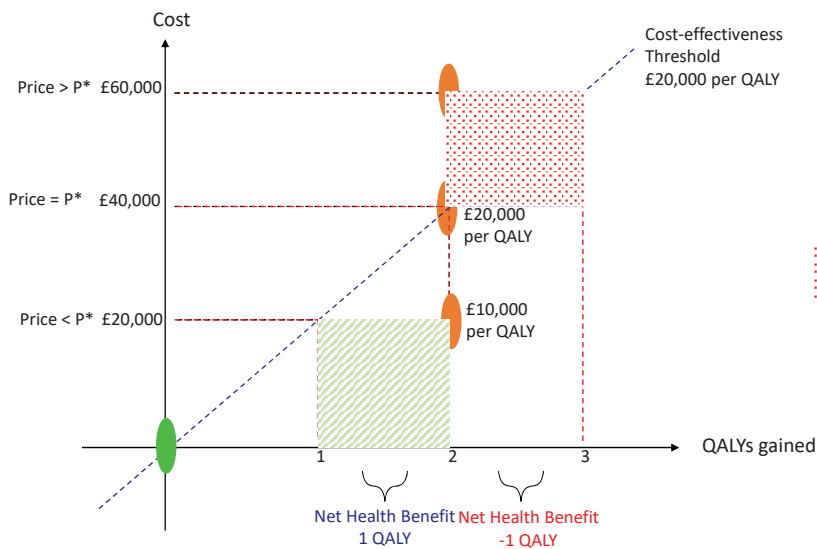



Q: What does this mean?

A: With its current budget and efficiency in producing health, if the health system budget was increased by \$20,000 it would produce ONE additional Quality Adjusted Life Year; but if the health system budget was reduced by \$20,000, it would produce ONE less Quality Adjusted Life Year.


3

Expected impact on health system sustainability



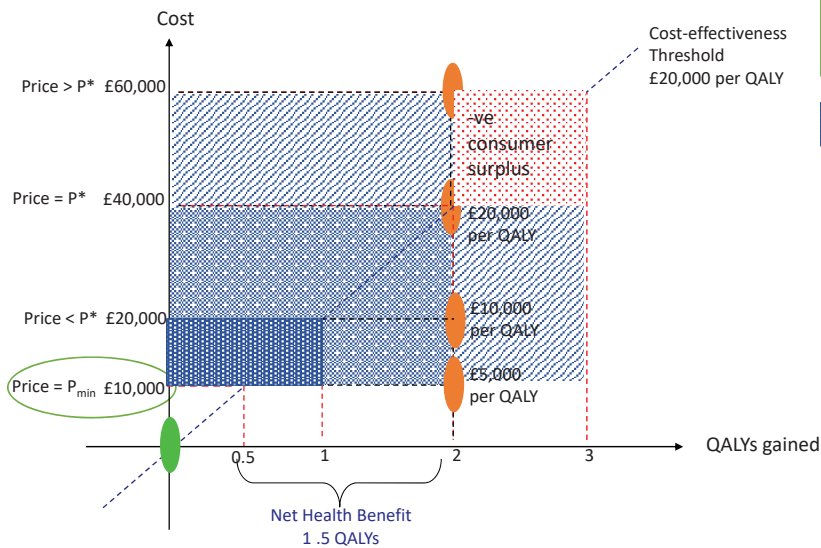
 = Difference between the maximum health system would be willing to pay (give up) for the technology and what it actually has to give up = Consumer Surplus

+ve consumer surplus contributes to health system sustainability

 -ve consumer surplus risks health system sustainability


4

Rewarding Innovation



P_{min} = price which just covers the costs of production.

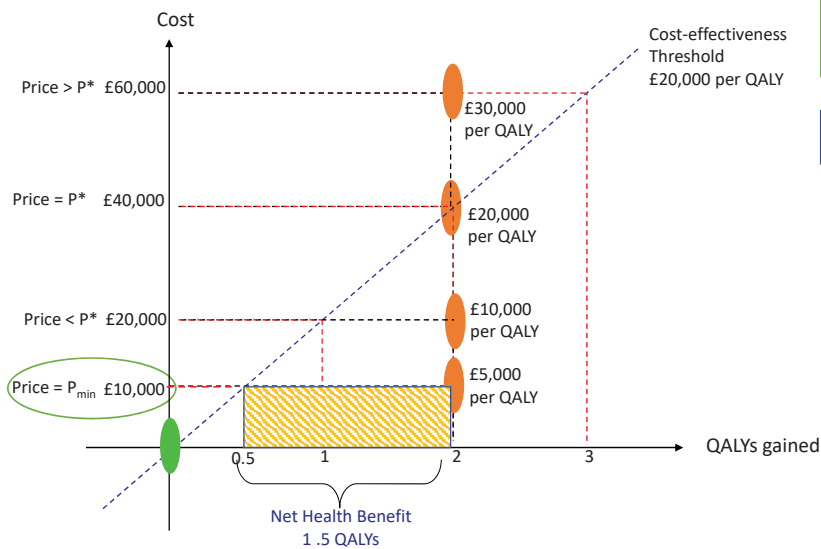
Price < P_{min} = Drug will not be supplied to the market.

 Difference between minimum price and the price received = Producer Surplus

Value of Innovation = Consumer Surplus plus Producer Surplus


5

Rewarding Innovation



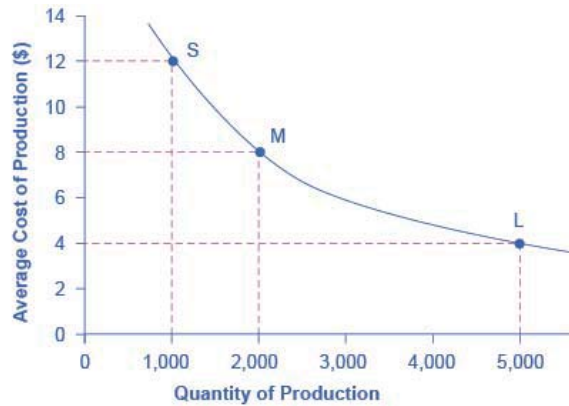
P_{min} = price which just covers the costs of production.

Price < P_{min} = Drug will not be supplied to the market.

 Welfare loss associated with drug not being supplied

6

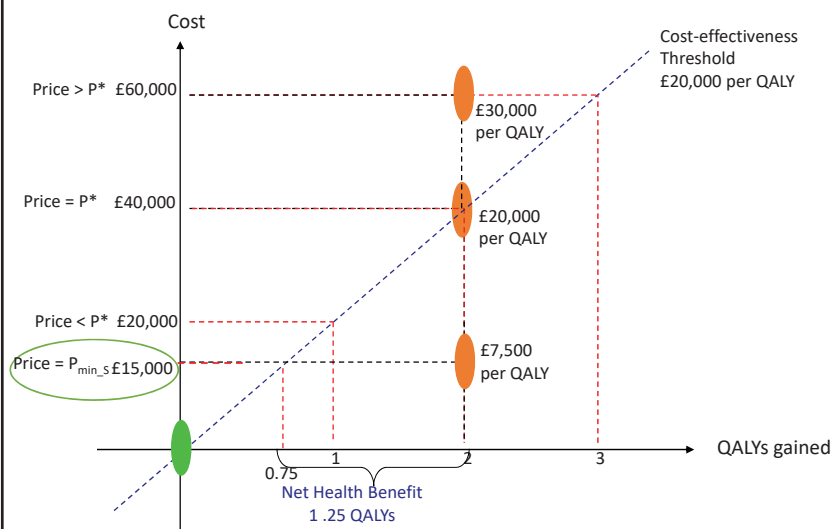
Unpacking market size: Market Size and Reserve Price (P_{\min})



© Khan Academy 2018

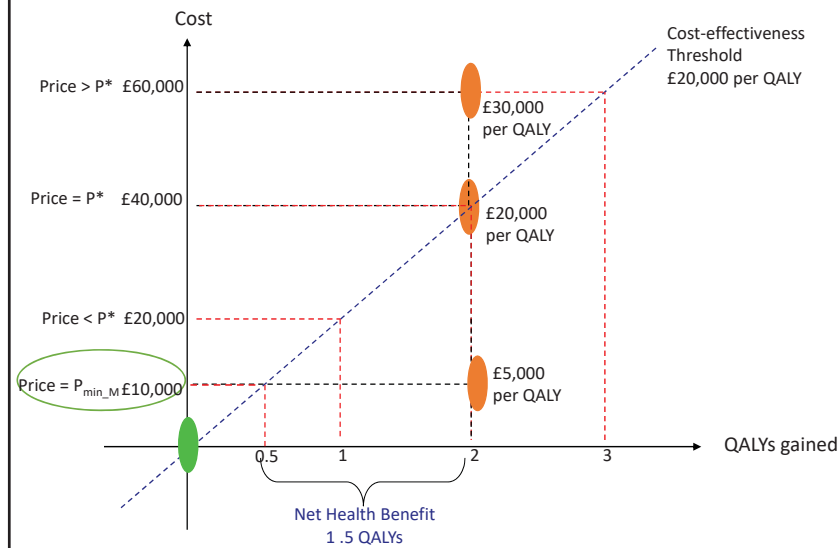
9

Market Size and Reserve Price: Orphan



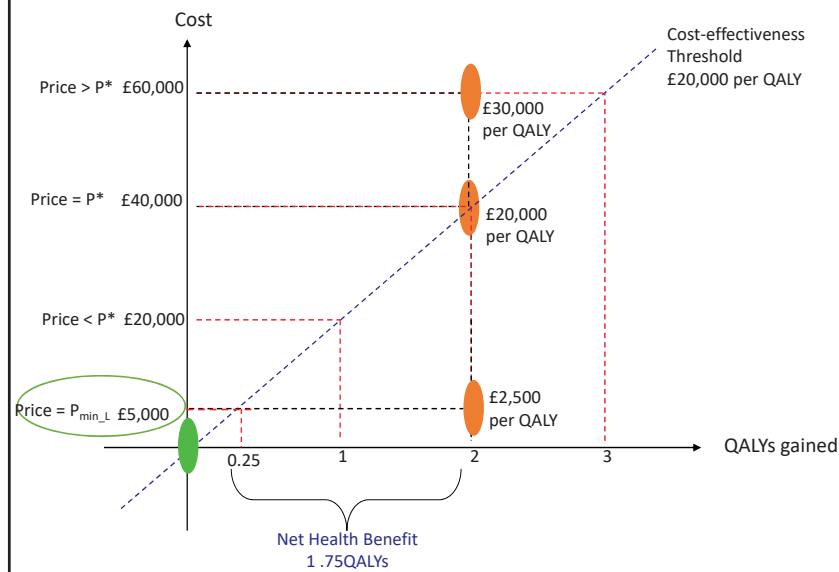
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Market Size and Reserve Price: Standard



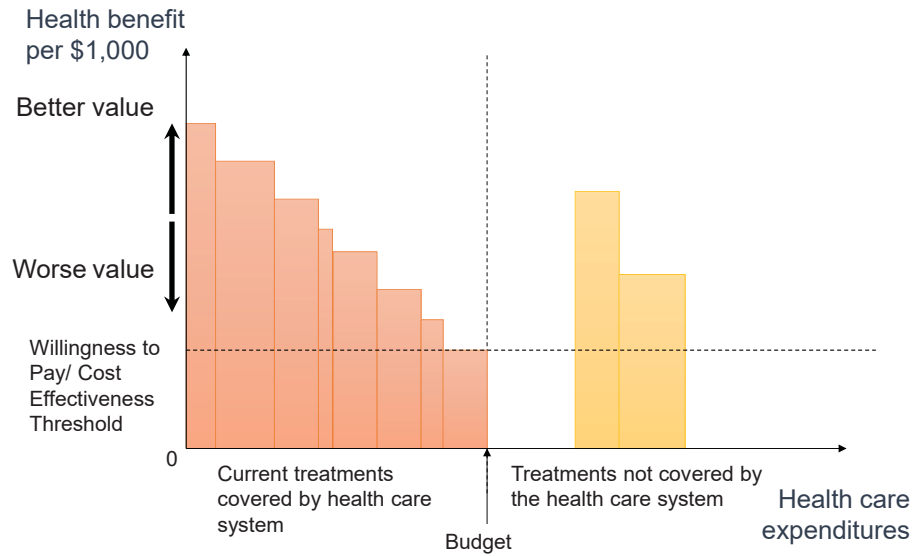
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Market Size and Reserve Price: Blockbuster



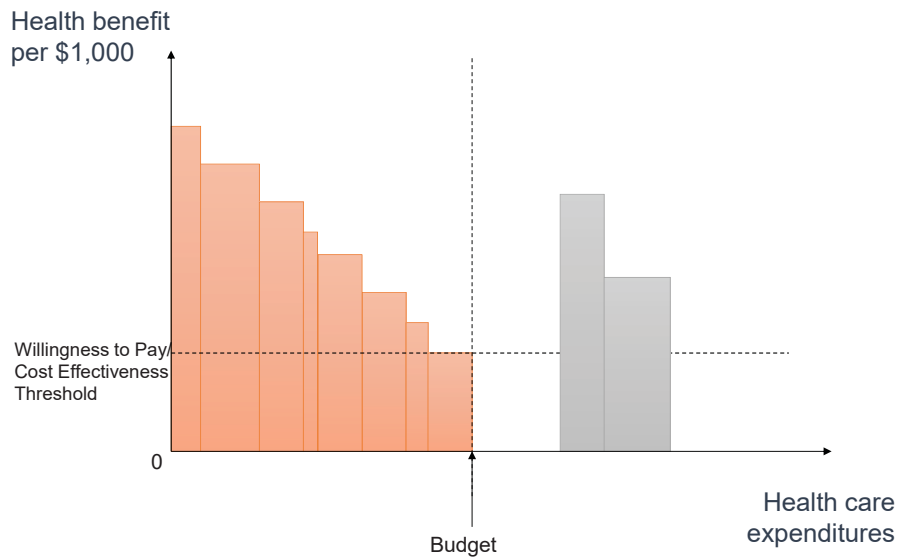
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Market size and budget impact



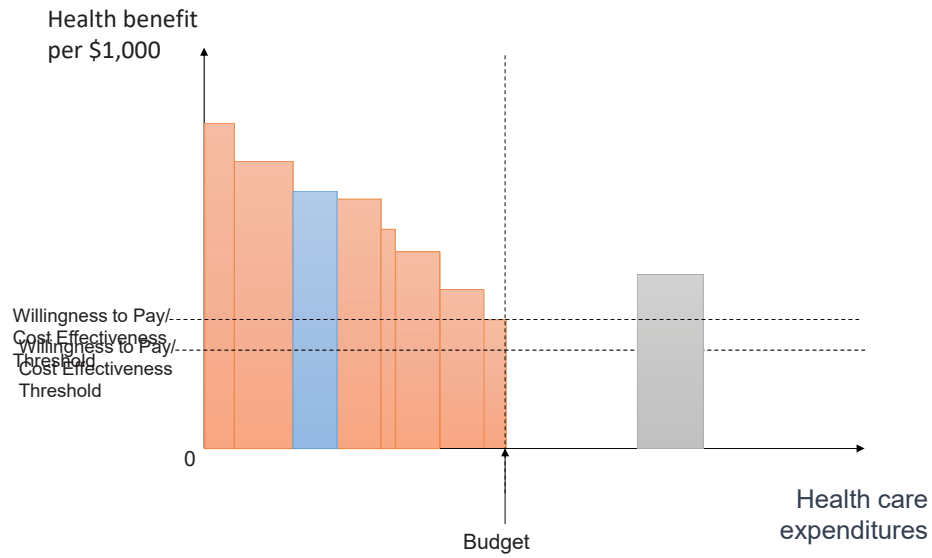
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Market size and budget impact



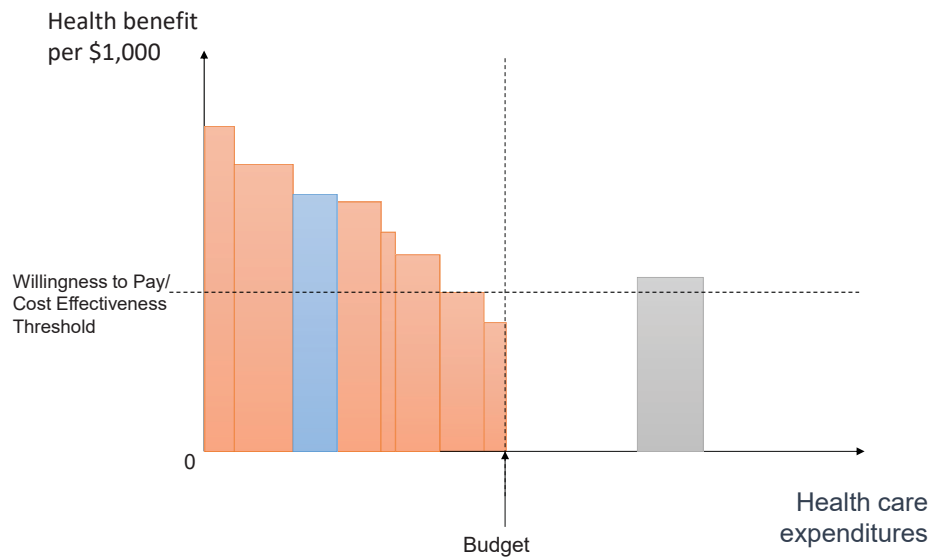
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Market size and budget impact



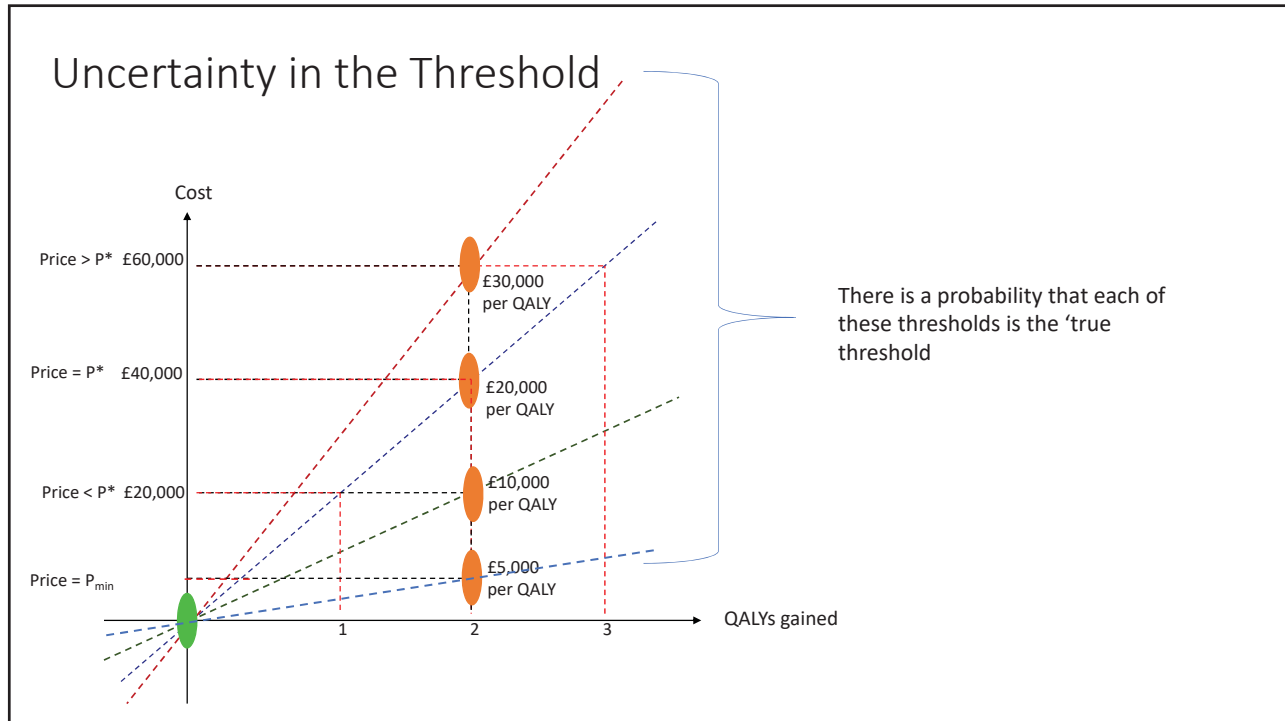
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Market size and budget impact



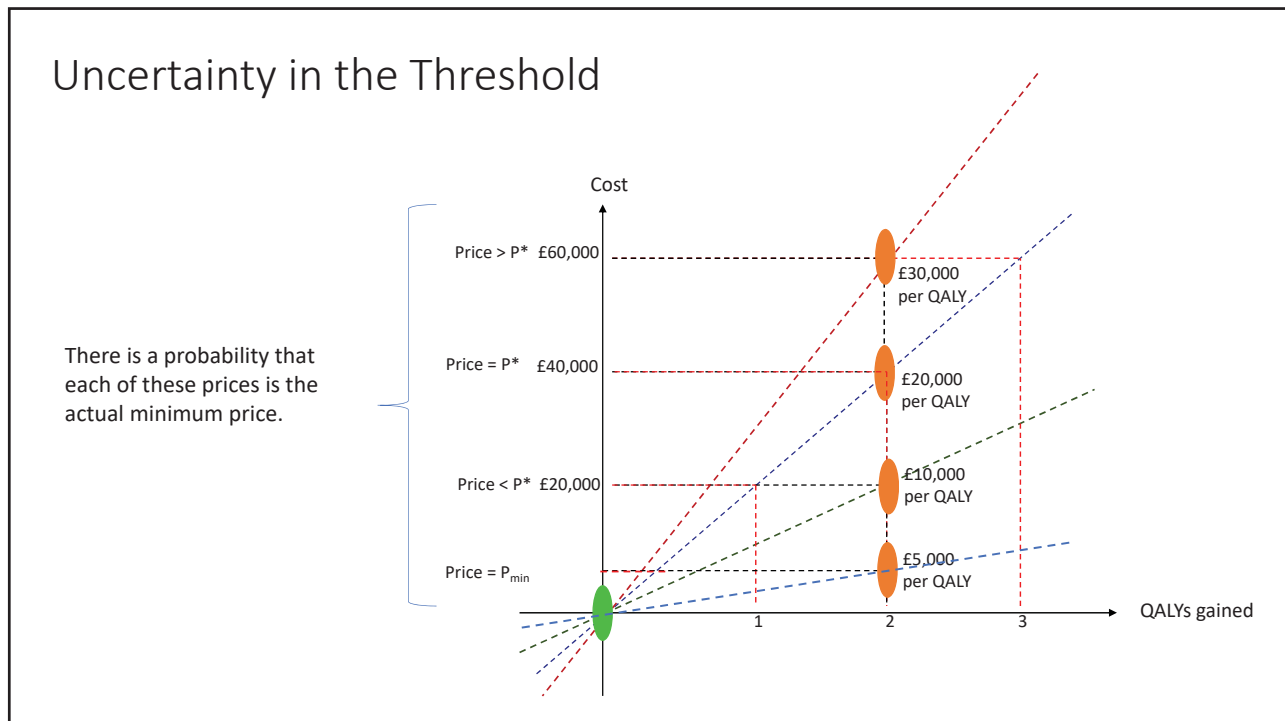
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Uncertainty in the Threshold



17

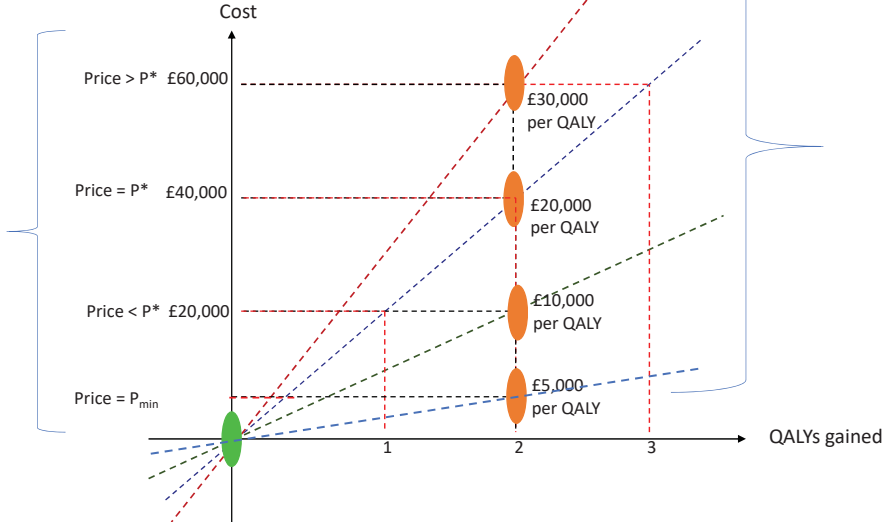
Uncertainty in the Threshold



18

Uncertainty in the Threshold

For any given ceiling price we can calculate and seek to minimise the expected value of the uncertainty (paying too much, paying too little, and losing access completely).



Appendix 2.5: Slides from 5 February 2019 (Dr Mike Paulden)

Note: The 'Draft Potential Recommendations' provided in these slides were discussed at the 5 February 2019 meeting. They were then revised, based on feedback from members, before a final set of 'Potential Recommendations' were voted on by the Working Group.

PMPRB Technical Working Group Meeting

5 February 2019

1

Conceptual Framework

- The role of the Working Group was to examine and make recommendations to the Steering Committee regarding a number of specific technical issues. The Terms of Reference specified six distinct areas of focus for the Working Group to consider.
- This Conceptual Framework was drafted by the Chair prior to the final meeting of the Working Group. Its purpose was to guide the Working Group in making consistent recommendations across all six of these areas of focus, while respecting the policy intent and the range of views expressed by members of the Working Group throughout their deliberations.

2

Economic principles

- At any given price, the 'economic surplus' from a good is the sum of two parts:
 - The 'consumer surplus', which is the benefit obtained by consumers because they are able to purchase the good at a price lower than their 'willingness-to-pay';
 - The 'producer surplus', which is the benefit obtained by producers because they are able to sell the good at a price higher than their 'willingness-to-accept'.
- In order to consider the consumer and producer surplus that might arise from the PMPRB setting a ceiling price on a new medicine, we must first specify demand and supply curves.

3

Demand curve for a medicine

- The demand curve reflects society's willingness-to-pay for the medicine in question.
- It is for the PMPRB, rather than members of the Working Group, to define the components of this demand curve. The Working Group therefore defers to the government's policy intent when considering the relevant components of the demand curve.

4

Policy intent

- During the Working Group’s deliberations, the PMPRB stated that the most appropriate perspective to adopt is that of *Canada’s publicly funded health care systems*.
- The ‘Regulatory Impact Analysis Statement’ (RIAS) (p.10) states that the *quality-adjusted life year (QALY)*, as used in cost-utility analysis, is regarded as the “gold standard” approach to considering the economic value of new medicines.
- In a July 2018 document prepared for the Working Group, the PMPRB clarified that the purpose of the PMPRB is to ensure that *patentees do not change excessive prices during the statutory monopoly period*.

5

Demand curve for a medicine

- In light of this policy intent, a reasonable specification of the demand curve for a new medicine is based upon the net impact upon the health of patients (as measured in QALYs) associated with adopting the medicine within Canada’s publicly funded health care systems for the duration of the statutory monopoly period.
- The net impact of a new medicine upon patient health is a function of two components:
 - The gain in health experienced by patients who receive the new medicine;
 - The loss in health experienced by other patients whose health care subsequently receives less funding than it would have done in the absence of the new medicine.

6

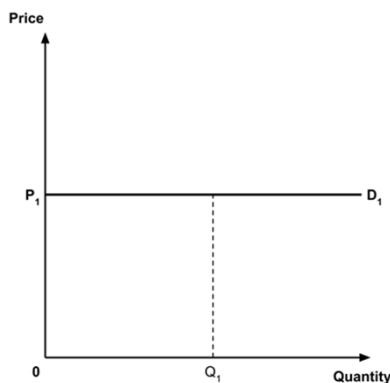
Equity weighting

- Although the Terms of Reference required the Working Group to consider potential approaches for allowing higher ceiling prices for some medicines on the basis of specific characteristics (so-called 'equity weighting'), it was agreed by the Working Group that insufficient empirical evidence exists to do this at the present time. For the purposes of this conceptual framework, equity weighting is therefore not applied.

7

Location of the demand curve

- The demand curve plots the ceiling price at which the incremental cost-effectiveness ratio (ICER) of the new medicine is equal to k



8

Supply curve for a medicine

- The supply curve plots the lowest price that a manufacturer would be willing to accept for a medicine. This is sometimes referred to as the 'reservation' (or 'reserve') price of the medicine.
- The supply curve is a function of a number of potential considerations, including the initial costs associated with developing the medicine, the marginal costs of production, and the potential implications for pricing in other jurisdictions as a result of 'reference pricing'.

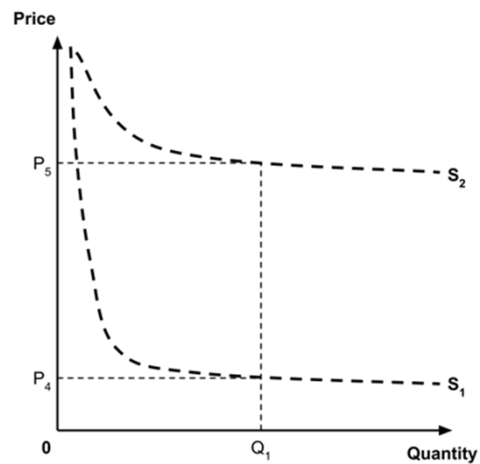
9

Supply curve for a medicine

- The components of the supply curve are complex.
- For the purposes of this framework, the medicine's supply curve will therefore be treated as unknown (and plotted as a dashed line).
- Despite being unknown, we may reasonably expect the supply curve for a medicine to have the following basic properties:
 - A relatively high intercept on the vertical axis, reflecting substantial initial costs associated with developing the medicine;
 - A downwards slope, reflecting a declining per-patient cost of supplying the medicine as the quantity supplied increases. This declining per-patient cost arises from the ability to spread the initial costs of development across a greater number of patients, and also potential economies of scale in the production of the medicine.

10

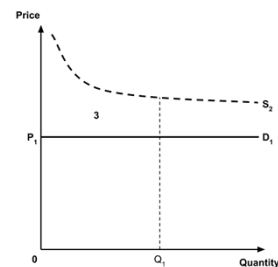
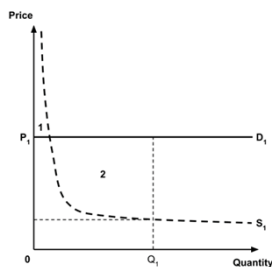
Supply curve for a medicine



11

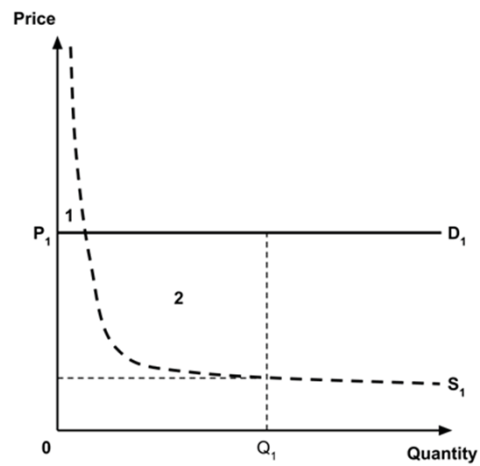
Economic surplus

- The economic surplus is illustrated by the area of the region below the demand curve and above the supply curve, minus any area above the demand curve but below the supply curve, and bounded between the vertical axis and the quantity of medicine adopted.



12

1. Producer receives entire surplus (P1)



13

2. Consumers receive entire surplus (P6)



14

Topic 1: Options for determining what medicines fall into 'Category 1'

- A Category 1 medicine is one for which a preliminary review of the available clinical, pharmacoeconomic, market impact, treatment cost and other relevant data would suggest is at elevated risk of excessive pricing.
- The following criteria have been identified as supporting a Category 1 classification:
 - a) The medicine is 'first in class' or a 'substantial' improvement over existing options
 - b) The medicine's opportunity cost exceeds its expected health gain
 - c) The medicine is expected to have a high market impact
 - d) The medicine has a high average annual treatment cost
- Should other criteria be considered? What are the relevant metrics for selecting medicines that meet the identified criteria and what options exist for using these metrics?

15

Topic 1: Summary of Deliberations

- Should other criteria be considered?
 - No additional criteria were suggested by members of the Working Group.
- What are the relevant metrics and what options exist for their use?
 - Criterion B is impractical to implement as a screen.
 - Criterion D should be 'incremental' upon existing treatment.
 - Definitions should reflect practice elsewhere, ideally based upon existing definitions.
 - 'Thresholds' should be clearly specified, to provide a 'clear bright line' for manufacturers.
 - Metrics should result in a manageable number of Category 1 medicines for the PMPRB.

16

Topic 1: Draft Potential Recommendations

1. **The PMPRB should not consider any additional criteria.**
2. **The PMPRB should remove Criterion B from consideration.**
3. **Criterion D should be ‘incremental’ upon existing treatment.**
4. **Metrics for criteria A, C and D should reflect existing Canadian practice (e.g. based on existing definitions of ‘substantial’ treatment benefit).**
5. **‘Thresholds’ for each criterion should be determined by the PMPRB, taking into account the capacity for assessing Category 1 medicines, the technical considerations of the Working Group, and the policy intent.**
6. **‘Thresholds’ for each criterion should be clearly specified, so as to provide a ‘clear bright line’ to manufacturers.**

17

Topic 2: Application of supply-side cost effectiveness thresholds in setting ceiling prices

- Potential approaches for implementing a price ceiling based on a medicine’s opportunity cost.
- Potential approaches for allowing price ceilings above opportunity cost for certain types of medicines (e.g. pediatric, rare, oncology, etc)

18

Topic 2: Summary of Deliberations (1/2)

- Potential approaches for implementing a price ceiling based on a medicine's opportunity cost
 - An estimate of the 'supply-side cost-effectiveness threshold' ('k') allows for estimation of the health opportunity cost, in terms of forgone QALYs, associated with new medicines.
 - Conceptually, the Working Group expects 'k' to vary across provinces and territories.
 - The only estimate of 'k' currently available for Canada is that by Ochalek et al. (2018), which estimated 'k' to be \$30,000 per QALY for Canada as a whole.
 - Concerns were raised about the instrumental variables (IVs) used for in this empirical work, and also the reliance upon UK (rather than Canadian) data.
 - Nevertheless, the \$30,000 per QALY estimate of 'k' by Ochalek et al. (2018) is in the same ballpark as recent empirical estimates of 'k' published in other PMPRB12 countries (UK: £12,936 per QALY, Australia: \$28,033 AUD per QALY, Spain: €24,870 per QALY).
 - Further empirical research is required to estimate 'k' in Canada - this should use Canadian data, appropriate IVs, and consider variation in 'k' across provinces/territories.
 - Any measure of opportunity cost used for setting a price ceiling should be clearly specified, so as to provide a 'clear bright line' for manufacturers.

19

Topic 2: Summary of Deliberations (2/2)

- Potential approaches for allowing price ceilings above opportunity cost for certain types of medicines (e.g. pediatric, rare, oncology, etc)
 - There is insufficient empirical evidence to implement 'equity weights' at the present time (as would be required to allow price ceilings above opportunity cost for some medicines).
 - There are technical considerations in implementing 'equity weights' in practice, including the need to respect horizontal equity by applying equity weights to all patients affected.
 - Applying equity weights to patients who bear the opportunity cost of new medicines requires an understanding of their characteristics, in addition to an estimate of the magnitude of health forgone (such that an estimate of 'k' is necessary but insufficient).
 - The PMPRB should support future empirical research in this area - this should estimate how 'demand side' willingness-to-pay for a QALY in Canada differs according to the characteristics of the patient, disease and/or technology in question.

20

Topic 2: Conceptual Framework

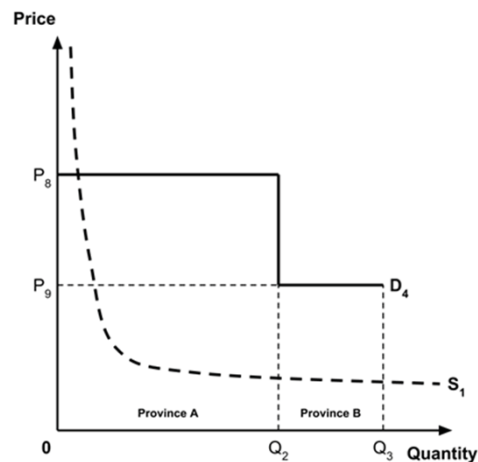
21

Pricing across provinces and territories

- Since provinces and territories in Canada have some autonomy in setting health care budgets and prioritizing spending, it follows that k would be expected to vary by province and territory.
- Since the demand curve plots the ceiling price at which the incremental cost-effectiveness ratio (ICER) of the new medicine is equal to k , it follows that the demand curve will be higher in provinces and territories with larger estimates of k .

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Pricing across provinces and territories



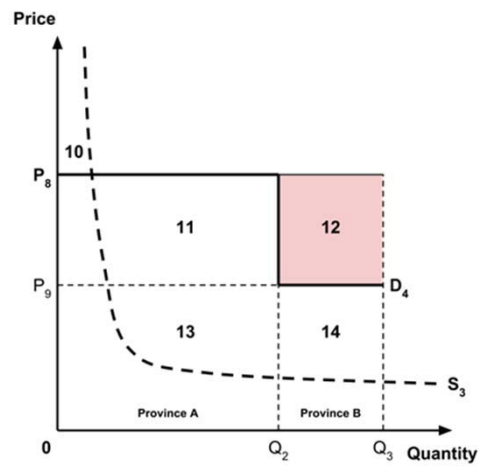
23

Approaches for setting a single ceiling price

- The Working Group considered several approaches for setting a single ceiling price across provinces and territories, including:
 1. A ceiling price at which the medicine is 'just' cost-effective in the province or territory with the highest k (such that the ICER equals this highest k);
 2. A ceiling price at which the medicine is 'just' cost-effective in the province or territory with the lowest k (such that the ICER equals this lowest k);
 3. A ceiling price at which the medicine is 'just' cost-effective across Canada as a whole (such that the ICER equals a 'weighted average' of k across Canada).

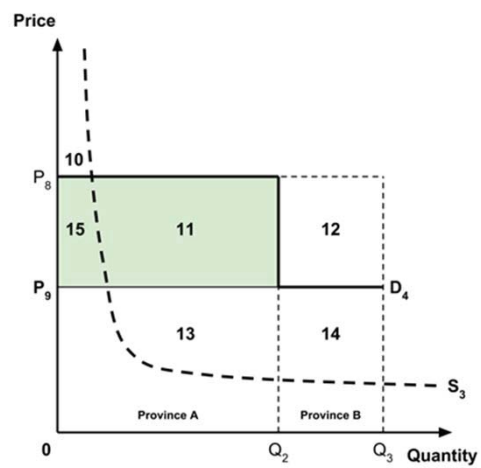
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Approach 1: Highest k



25

Approach 2: Lowest k



26

Objective 1: No health loss across Canada

- The first approach is inconsistent with this policy objective. This is because this approach results in diminished population health (negative consumer surplus) in all provinces and territories except that with the highest k (in which consumer surplus is zero), resulting in diminished population health (negative consumer surplus) overall.
- The second approach comfortably satisfies this policy objective (since it results in positive overall consumer surplus), while the third approach only just satisfies this policy objective (since it results in an overall consumer surplus of zero).

29

Objective 2: No health loss in any province

- Both the first and third approaches are inconsistent with this policy objective. This is because both approaches result in diminished population health (negative consumer surplus) in at least one province or territory.
- The second approach would only just satisfy this policy objective, since consumer surplus is zero in the province or territory with the lowest k .

30

Objective 3: Max health gain across Canada

- Consideration should be given to the location of the supply curve.
- Since the location of the supply curve is uncertain, this is challenging.
- Key assumption: a medicine will not be launched if producer surplus is negative.
 - If a medicine is not launched, the pharmacoeconomic value is zero since there is no resulting net gain in QALYs.
 - For the pharmacoeconomic value to be positive, the medicine must be launched at a ceiling price that results in positive consumer surplus.
- *The mandate of the PMPRB is to protect consumers from excessive pricing, not to ensure that products are launched into the market.*

31

Objective 3: Max health gain across Canada

- If the supply curve is understood to be sufficiently low that the medicine would be profitable at the ceiling price arising under the second approach (P9), then maximizing population health requires setting a ceiling price below P9, so as to maximize consumer surplus subject to producer surplus being non-negative.
- However, since the true location of the supply curve is uncertain, any reduction in the ceiling price carries a risk that producer surplus might become negative, such that the medicine would not launch at all. In such circumstances, consumer surplus would be zero, whereas at a higher ceiling price of P9 the new medicine would have launched and consumer surplus would have been positive.

32

Topic 2: Draft Potential Recommendations

1. The Working Group regards the current evidence base with respect to the opportunity cost of adopting new medicines within Canada's public health care systems as highly uncertain. The PMPRB should be aware of limitations with the empirical work by Ochalek et al. (2018), including the reliance on UK data and the choice of instrumental variables (IVs) used. However, the direction of any resulting bias is unknown. Furthermore, the authors' \$30,000 per QALY estimate of 'k' is in line with published empirical estimates of 'k' for other PMPRB12 countries.
2. The PMPRB should support further empirical research to estimate a 'supply-side cost-effectiveness threshold' ('k') for Canada. This research should consider and report on potential variation in 'k' across provinces and territories.
3. There is insufficient empirical evidence to implement 'equity weights' at the present time, as would be required to allow price ceilings above opportunity cost for some medicines but not others.
4. Any determinants of the price ceiling should be clearly specified, so as to provide a 'clear bright line' to manufacturers.

33

Topic 3: Medicines with multiple indications

- Options for addressing medicines with multiple indications (e.g. multiple price ceilings or a single ceiling reflecting one particular indication).

34

Topic 3: Summary of Deliberations

- Indication-specific pricing is desirable in principle, since it would allow the price of each medicine to more closely reflect the medicine's value to patients in each indication.
- However, other countries which have implemented indication-specific pricing have a sophisticated IT infrastructure to support this, which Canada lacks.
- As a result, it is not feasible to implement indication-specific pricing in Canada at the present time.
- Rebenching of prices over time causes instability and uncertainty for manufacturers.
- Since manufacturers may choose the order in which indications are launched, and may avoid launching in specific indications altogether, any approach to pricing across indications may give rise to concerns of 'gaming' by manufacturers.

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Topic 3: Conceptual Framework

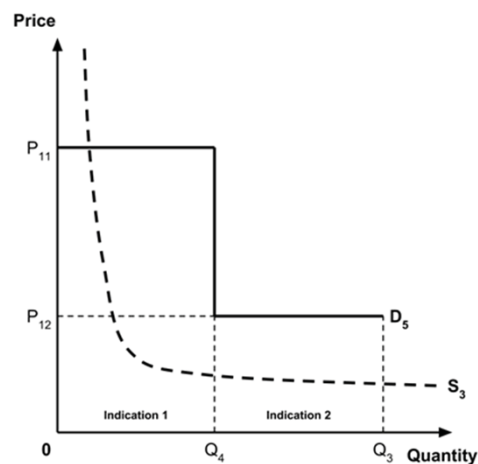
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Pricing across indications

- Where a medicine is available for multiple indications, this has implications for specification of the demand curve for a new medicine.
- If the per-patient health gain from the new medicine is different in each indication, then the ceiling price at which the ICER is equal to k will also differ across indications.
- It follows that the demand curve will generally be different for each indication, with a relatively higher ceiling price corresponding to an ICER of k for those indications in which the medicine has a relatively greater per-patient health gain.

37

Pricing across indications



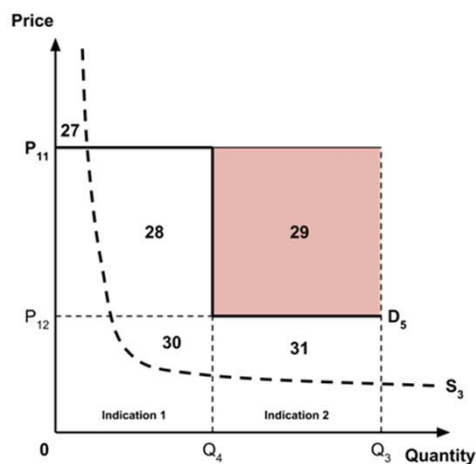
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Approaches for setting a single ceiling price

- The Working Group therefore considered various approaches for setting a single ceiling price across multiple indications, including:
 1. A ceiling price at which the medicine is 'just' cost-effective in the most cost-effective indication (such that the ICER equals k in this indication);
 2. A ceiling price at which the medicine is 'just' cost-effective in the least cost-effective indication;
 3. A ceiling price at which the medicine is 'just' cost-effective across all indications (such that a 'weighted average' of the ICER across all indications equals k);
 4. A ceiling price at which the medicine is 'just' cost-effective in the first indication considered by the PMPRB (such that the ICER equals k in this indication).

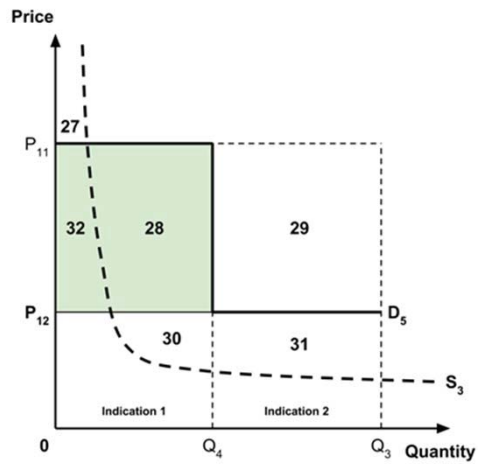
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Approach 1: Most cost-effective indication



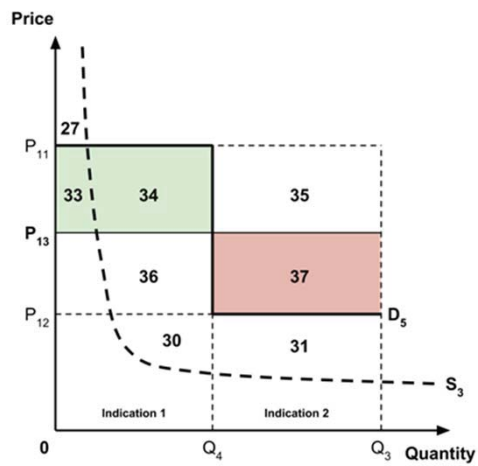
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Approach 2: Least cost-effective indication



41

Approach 3: 'Weighted average' of indications



42

Approach 4: First indication considered

- This approach is the simplest to administer, since it does not require rebenching of ceiling prices in future if and when additional indications are launched.
- However, because producer surplus is unambiguously greater at a ceiling price of P_{11} than P_{12} , this approach provides an incentive for the manufacturer to launch in the most cost-effective indication first to secure a higher ceiling price for future indications.

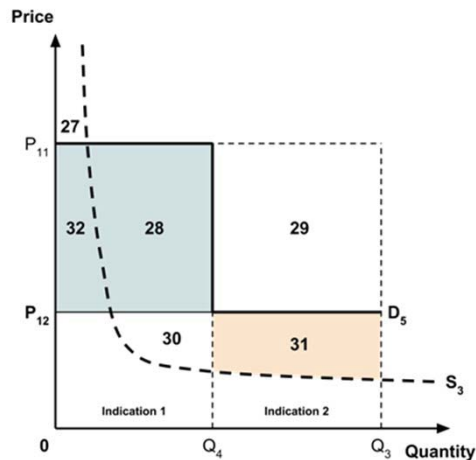
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Approach 4: First indication considered

- If manufacturers act upon this incentive and are perfectly strategic, then this approach would have the same implications for consumer surplus as Approach 1.
- If manufacturers do *not* act upon this incentive, then in some cases consumer surplus from additional indications will be positive (if a less cost-effective indication is launched first) and in other cases consumer surplus from additional indications will be negative (if a more cost-effective indication is launched first). If the decision as to which indication to launch first is truly random, then a reasonable expectation would be that the *expected* consumer surplus associated with additional indications is zero. This would have equivalent implications for consumer surplus as Approach 3.
- It follows that this approach may be considered as lying somewhere between Approach 1 and Approach 3, with expected consumer surplus ranging between negative (if manufacturers are in any way strategic) to zero (if manufacturers are not strategic at all).

44

Potential for strategic behaviour



45

Objective 1: No health loss across Canada

- The first approach is inconsistent with this policy objective
- The second approach comfortably satisfies this policy objective (since it results in positive overall consumer surplus)
- The third approach only just satisfies this policy objective (since it results in an overall consumer surplus of zero)
- The fourth approach satisfies this policy objective *if manufacturers are not strategic*, but if manufacturers behave strategically then the expectation would be that consumer surplus is negative overall, in which case this approach would *not* satisfy this objective.

46

Objective 2: No health loss in any indication

- Both the first and third approaches are inconsistent with this policy objective. This is because both approaches result in diminished population health (negative consumer surplus) in at least one indication.
- The second approach would only just satisfy this policy objective, since consumer surplus is zero in one indication and positive in all others.
- The fourth approach satisfies this policy objective *if manufacturers always launch in the least cost-effective indication first*, otherwise it does not satisfy this objective

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Objective 3: Max health gain across Canada

- The most desirable ceiling price under this policy objective is the lowest ceiling price at which producer surplus is non-zero.
- Depending upon the location of the supply curve, this might be at a ceiling price below P_{12} , leading to greater consumer surplus than that resulting from any of the four approaches considered above.
- However, as before, lowering the ceiling price to extract additional consumer surplus carries a risk that producer surplus may become negative, such that the medicine is not launched and consumer surplus is zero.

48

Topic 3: Draft Potential Recommendations

- 1. Since indication-specific pricing is not currently feasible, the PMPRB should specify a single ceiling price for each medicine that applies across all indications.**
- 2. This ceiling price should be consistent with the government's policy intent with regards to the allocation of consumer and producer surplus.**
- 3. The PMPRB should support efforts to develop the necessary infrastructure to allow for indication-specific pricing in future.**

49

Topic 4: Accounting for uncertainty

- Options for using the CADTH and/or INESS reference case analyses to set a ceiling price.
- Options for accounting for and/or addressing uncertainty in the point estimate for each value-based price ceiling.

50

Topic 4: Summary of Deliberations

- Options for using the CADTH and/or INESSS reference case analyses to set a ceiling price
 - CADTH guidelines (4th edition) describes principle methods, but differences between the CADTH and INESSS reference cases, and between each analyst's consideration of uncertainty, may lead to different point estimates of the ICER
 - PMPRB could specify its own 'reference case', including a preferred 'threshold' & perspective
 - PMPRB could set up a committee to review the economic evidence
 - Price adjustments may be needed as real world evidence changes
- Options for accounting for and/or addressing uncertainty in the point estimate for each value-based price ceiling.
 - CADTH currently reports a range for the reference case ICER, not a point estimate
 - 'Price reduction tables' reported by CADTH not subject to peer review
 - CADTH methods (4th edition) mandate probabilistic analysis
 - Use the expected values or the upper/lower end of the range?

51

Topic 4: Conceptual Framework

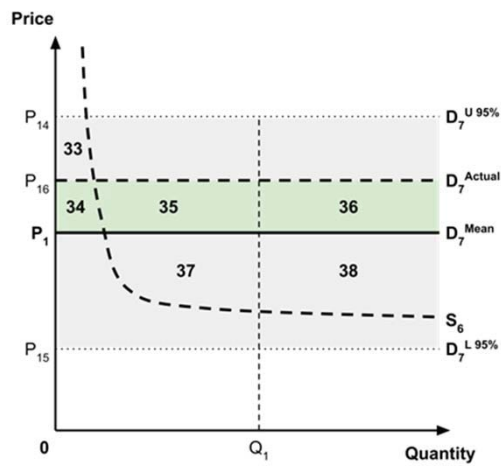
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Uncertainty



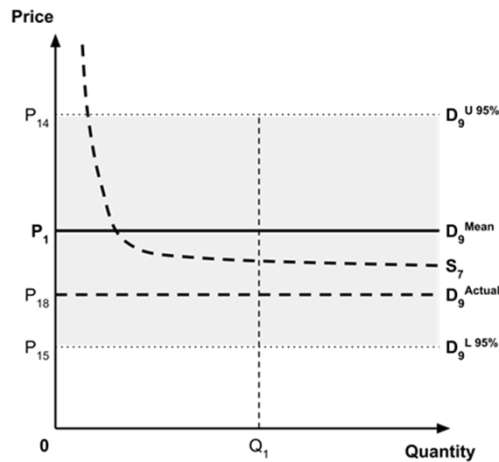
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Actual demand curve higher, drug launched



54

Actual demand curve lower, not launched



57

Implications of uncertainty

- If the medicine is launched at a ceiling price coinciding with the expected demand curve then the expected consumer and producer surplus is zero.
- If the medicine is unprofitable at a ceiling price coinciding with the expected demand curve, and is also unprofitable at a ceiling price coinciding with the actual demand curve, then consumer surplus is zero.
- If the medicine is unprofitable at a ceiling price coinciding with the expected demand curve, but would have been profitable at a ceiling price coinciding with the actual demand curve, then the impact of uncertainty is to diminish the total economic surplus such that the impact upon expected consumer surplus at a ceiling price coinciding with the expected demand curve is negative.

58

Value of information analysis

- In conventional pharmacoeconomics, the expected loss that results from uncertainty is estimated using 'value of information' (VOI) analysis.
- Since the focus of conventional pharmacoeconomic analysis is making a yes/no decision regarding adoption of a new medicine, conventional VOI analysis considers the expected loss associated with making the 'wrong' decision (e.g. approving a medicine that would otherwise have been rejected, or *vice versa*).
- In the context of the PMPRB using 'pharmacoeconomic value' as a factor when considering the ceiling price for a new medicine, the expected loss as a result of uncertainty comes not from making the 'wrong' yes/no decision, but from setting the 'wrong' ceiling price.

59

Value of information analysis

- In principle, VOI analysis could be used to estimate this expected loss, and hence the value associated with obtaining additional sample information for one or more uncertain parameters. The results of these analyses could then be used to apply a reduction to the ceiling price of the medicine to reflect the diminished expected pharmacoeconomic value as a result of uncertainty.
- However, conducting such VOI analyses would require an understanding of the location of the supply curve, since this is required to estimate the expected loss in economic surplus, and in practice the location of the supply curve is unknown. Although, in principle, the supply curve could be modelled with a probability distribution in order to permit VOI analysis to take place, methods for estimating the parameters of such a distribution are undeveloped. It may therefore be infeasible to conduct VOI analyses of this type at the present time.

60

Topic 4: Draft Potential Recommendations

- 1. The PMPRB should consider its attitude towards risk**
- 2. If the PMPRB is risk-neutral, the *expected* values of the incremental costs and QALYs and k should be used when considering the ceiling price**
- 3. If the PMPRB is *not* risk-neutral, values above or below the expected values may be appropriate, depending upon the risk attitude**
- 4. The value of obtaining additional information for uncertain parameters should not be routinely considered by the PMPRB at the present time**

61

Topic 5: Perspective

- Options to account for the consideration of a public health care system vs societal perspective, including the option of applying a higher value-based price ceiling in cases where there is a 'significant' difference between price ceilings under each perspective.
- How to define a 'significant' difference in price ceilings between each perspective.

62

Topic 5: Summary of Deliberations

- **PMPRB intervened to state that public payer perspective is preferred**
- Prior to this, the Working Group considered how reforms have implications for private payers and individuals paying out of pocket
- A broad 'societal' perspective is problematic for reasons of principle (e.g. equity) and practicality (specifying productivity, spillover effects, caregiver burden, etc.)
- Concern that excluding productivity would impact private payers
- Cash paying customers will be excluded from the confidential MRP ceiling price
- Benefits to private payers might not be transferred back to end users

63

Topic 5: Draft Potential Recommendations

1. **Given the policy intent, the public payer perspective should be adopted**
2. **The PMPRB should be aware of the potential implications of its reforms for private payers and individuals**

64

Topic 6: Application of the market size factor in setting ceiling prices

- Approaches to derive an appropriate affordability adjustment to a medicine's ceiling price based on an application of the market size and GDP factors (e.g. based on the US 'ICER' approach).

65

Topic 6: Summary of Deliberations

- Different payers have different tolerances for expenditure growth
- In the UK, NICE recently agreed to cap expenditure growth on new medicines by 2% per annum
- Members considered the US ICER approach, which moved away from considering GDP factors when setting prices
- Market size is distinct from 'net budget impact'
- Particular implications for whether orphan drugs are profitable
- Market size not always known at launch (uncertainty)

66

Topic 4: Conceptual Framework

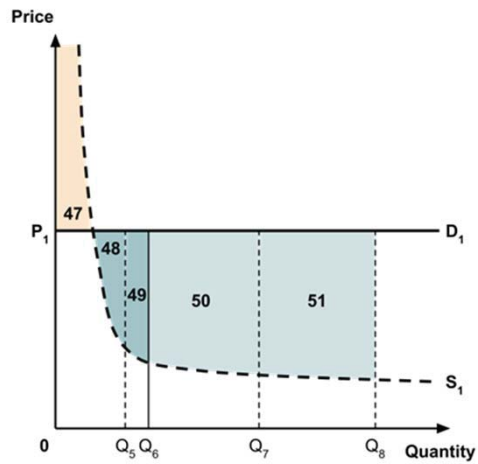
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Market size

- The PMPRB has proposed that a 'market size adjustment' may be applied to the ceiling price for some Category 1 medicines. This includes a potential upwards ceiling price adjustment for medicines with small market size and (independently) a potential downwards ceiling price adjustment for medicines with large market size.
- The first of these would have the effect of increasing the producer surplus (at the expense of consumer surplus) for medicines with small market size. The second would increase the consumer surplus (at the expense of producer surplus) for medicines with large market size.

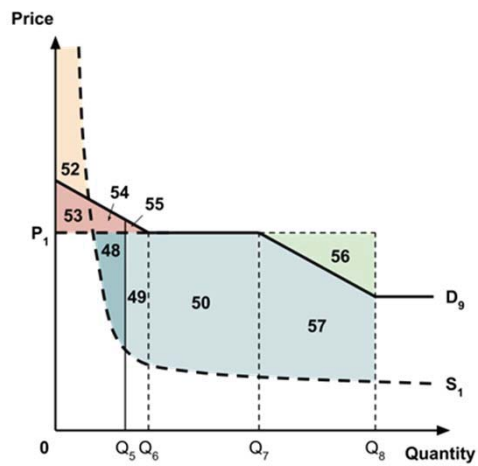
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Without market size adjustment



69

With hypothetical market size adjustment



70

Implications of a market size adjustment

- Increased consumer surplus from medicines with large market size
 - The reduction in the ceiling price for medicines with large market size results in an increase in consumer surplus and a reduction in producer surplus
- Reduced consumer surplus from medicines with small market size
 - A higher ceiling price for medicines with small market size results in greater producer surplus and a loss in consumer surplus
 - Since (in this example) consumer surplus was zero prior to the market size adjustment, consumer surplus is now negative for medicines with small market size.
- Increased profitability for medicines with small market size
 - Medicines with a market size between Q5 and Q6, which were unprofitable prior to the market size adjustment, now have positive producer surplus.
 - This might result in greater access to medicines with small market size.

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Potential risks and disincentives

- If the reduction in ceiling price for medicines with large market size is large, then manufacturers may be incentivized to reduce the quantity supplied so as to avoid the reduction in the ceiling price. This risk is particularly acute if the medicine in question has multiple indications, and if pricing across all indications is based upon the least cost-effective indication - as discussed earlier, this pricing approach might already provide an incentive for manufacturers to avoid launching in one or more indications, and the addition of a market size adjustment might exacerbate this risk.
- By providing a higher ceiling price for medicines with low market size, a market size adjustment would also relatively incentivize the development of such medicines. Over time, a reduction in medicines with large market size and an increase in medicines with small market size might result in progressively smaller gains and progressively larger losses in consumer surplus as a result of the market size adjustment.

72

Topic 6: Draft Potential Recommendations

- 1. The PMPRB should ensure that any market size adjustment results in the MRP changing smoothly with the market size**
- 2. The PMPRB should consider the implications for consumer and producer surplus, and ensure these are consistent with the policy intent.**
- 3. The PMPRB should consider potential disincentives that might result from application of a market size adjustment**

Appendix 3: 'On The Record' Comments

Appendix 3.1: Email from Frédéric Lavoie and Geoff Sprang (1/4)

Subject: Working Group meeting of July 26, 2018

Date: 9 August 2018 at 15:21 MST

From: Frédéric Lavoie

To: Mike Paulden

Cc: Geoff Sprang

Dear Mike,

On behalf of BIOTECanada and Innovative Medicines Canada, we would like to thank you for chairing the first face to face meeting of the PMPRB Working Group held on July 26, 2018. Although the industry associations we represent do not support the use of economic factors such as cost-effectiveness analyses as part of the proposed amendments to the Patented Medicines Regulations, and are also concerned about the initiation of Guidelines consultations before the finalization of regulatory changes, we felt that you were open to our points of view and invited us with the upmost respect to contribute throughout the meeting.

As the Working Group terms of reference stipulate that points of contention will be recorded by the Chair and reflected in the Working Group final report, we felt it would be appropriate to summarize our perspectives in writing and to provide you with our views on the discussions during the meeting.

Observations on the discussions:

We perceived during the meeting with the academic experts and other stakeholders represented at the Working Group that consensus cannot be achieved for the implementation of economic factors for the purpose of setting price ceilings for patented medicines in Canada. The debates that we observed around the table reinforced the apprehension our industry has communicated regarding the use of pharmacoeconomic factors, and made it clear that it is imperative for the Working Group to communicate to the Steering Committee and to the Federal Government the challenges presented by the proposed use of these factors, so that the scope of discussions with our industry and other stakeholders can be extended to include the consideration of alternative regulatory approaches as quickly as possible.

Determination of a willingness to pay threshold and the use of pharmacoeconomic factors at the PMPRB level:

When it comes to economic factors such as pharmacoeconomics, the proposed utilization of a threshold and of a cost-utility point estimate in the process involving Category One products (as first disclosed by the PMPRB to stakeholders on June 25th, 2018) would produce tremendous uncertainty and is therefore unacceptable.

The different schools of thought and academic debates around the establishment of a willingness to pay threshold through supply side or demand side methods are diverse and evolving. Even if an academic consensus were achievable, the implantation of a single method would always lead to a point estimate around which a distribution of possible results would reflect the high degree of uncertainty that exists regarding the establishment of a willingness to pay threshold and its variability across the diversity of Canadian perspectives it needs to reflect. Citing the work of Neumann et al. on this topic reflects this point: "Searching for a single benchmark is at best a quixotic exercise because there is no threshold that is appropriate in all decision contexts." (N ENGL J MED 371;9, August 28, 2014).

The same issue arises from the assessment of cost utility where substantial variability exists around the numerator and the denominator of the cost utility ratio compounded by the variability observed as a function of the analyst that produces the assessment and the peer reviewers that challenge the analyses (i.e. industry, CADTH, INESSS, the private sector, etc.). A review of recent CADTH CDR and pCODR recommendations conducted by Innovative Medicines Canada and EY shows that the degree of divergence between the cost-utility thresholds produced by CADTH versus those submitted by industry is significant: ICURs based on CADTH reassessment are significantly higher than those submitted by the manufacturers in the majority of cases; with the difference being as high as two to three times in many cases. The distribution of possible results around these point estimates is invariably wide and it is therefore inappropriate as a metric for setting the price ceilings of patented medicines. In addition, the perspective employed in CADTH CDR or pCODR submissions is a public drug plan perspective in accordance with the guidance provided by CADTH, and it is inappropriate to apply these pharmacoeconomic analyses to the entire Canadian population.

Given these significant limitations, it is inadvisable to use such an imprecise test of cost utility, compared against an equally controversial willingness to pay threshold, to determine a price ceiling for an innovative medicine. Its usage will lead to frequent and potentially litigious disputes requiring human and financial resources that are best deployed elsewhere by both the regulator and the regulated.

Furthermore, as many of our member companies operate on a global scale and have limited resources to allocate to meet the significant tasks required to bring a product to any individual market around the world, the regulatory signals sent by individual countries need to be as clear as possible to incentivize companies to launch innovative medicines. Contrary to the stated

objective of PMPRB's proposed new framework, the proposed set of economic factors will provide no "bright line" that will "yield ceiling prices that are foreseeable to patentees". Under such uncertain circumstances, it is foreseeable that many companies will delay or even forgo the launching of new innovative medicines in Canada.

Risk categorization:

The categorization exercise proposed by the PMPRB is only notionally consistent with the industry's proposal for a risk-based approach to pricing regulatory scrutiny. As was evident from the Working Group discussions, the identification application of specific criteria must be the subject of careful consideration to avoid unintended consequences. If the categorization is too broadly defined, as was the case with the initial information disclosed by PMPRB to stakeholders on June 25th, 2018, the number of patented medicines that will be subject to an elevated level of regulatory scrutiny will be too large. This in turn will impose a significant operational burden on both the regulator and the regulated, while failing to achieve the stated policy objective of focussing regulatory resources where they add the most value. Furthermore, this categorization needs to be correlated with the magnitude of the risks that concern policy makers. The PMPRB has not offered a compelling policy rationale for each of the proposed screening criteria. From the discussion at the Working Group, we believe that the potential impact of including these criteria requires further evaluation.

Once again, we thank you for listening to our perspective on behalf our industry associations, and for ensuring that the content of this communication is reflected in the proceedings of the Working Group and also communicated back to the Steering Committee.

We look forward to a continued constructive dialogue with you and the Working Group.

Frederic and Geoff

Appendix 3.2: Email from Frédéric Lavoie and Geoff Sprang (2/4)

Subject: Draft summary of 26 July Working Group meeting

Date: 17 August 2018 at 11:17 MST

From: Frédéric Lavoie

To: Mike Paulden, Chris Cameron, Christopher McCabe, Donald Husereau, Doug Coyle, Karen Lee, Maureen Smith, Patrick Dufort, Peter Jamieson, Stuart Peacock, Tammy Clifford, Tania Stafinski

Cc: Edward Burrows, Douglas Clark, Guillaume Couillard, Isabel Jaen Raasch, Matthew Kellison, Nelson Millar, Richard Lemay, Tanya Potashnik, Theresa Morrison, Geoff Sprang

Dear Mike,

We wanted to draw your immediate attention to some issues regarding the minutes.

After we sent you by email on August 9, 2018 (attached for reference) a summary of our industry perspectives and our views on the discussions during the first meeting of the technical working group (TWG), we have become aware that meeting minutes from the first meeting of the TWG have been shared with the PMPRB Steering Committee in advance of those minutes being shared and validated with the working group members themselves. As the terms of reference of the TWG stipulates that “the chair shall have final say on all matters of governance and procedures” we feel important to request that certain governance processes be improved. One such usual and customary process is that meeting minutes be reviewed and approved by committee members before they become more broadly circulated. We also recommend the minutes include more detail including time, date, duration of meeting, who was in attendance, who was unable to attend, provide a record of what was said, what was agreed to, and list action items and their status.

Furthermore, in this case, it is particularly problematic because the minutes, in our view, and as confirmed by the observations we shared with you by email on August 9, 2018, do not accurately or completely reflect the discussions of the working group, which could mislead the reader regarding the degree of expert consensus on fundamental issues under consideration. This gap in the minutes limits the ability of external stakeholders to the TWG (i.e. PMPRB steering committee members) to understand the origin and rationale of the points of contention that the chair is required to record in the final report of the TWG (as per terms of reference).

As examples of the issues of concern to us, we would draw your attention to the following

passages:

- “Several members expressed the view that the opportunity cost of a drug may not be an appropriate tool for screening purposes. It was suggested further study may be needed to inform the discussion. Members generally agreed that application of supply-side cost effectiveness thresholds were an appropriate approach to consider opportunity cost when setting ceiling prices for Category 1 drugs”
 - In our view, there was no general agreement on cost effectiveness thresholds as an appropriate approach to consider opportunity cost and the TWG never resolved the issue of how such a threshold could be determined. There was in fact considerable debate and disagreement on this, leading to PMPRB Chair Mitch Levine to question potential alternatives to the use of pharmacoeconomics. This lack of consensus was evident from your proposal (and the PMPRB staff’s agreement) to schedule additional conference calls beyond what was planned in the terms of reference to allow for further discussion and to arrive at more aligned views.
- “Members discussed using the CADTH and/or INESSS reference case analysis to set a price ceiling, as well as potential approaches to take in situations where the existing reference case was not relevant.”
 - We would note that the meeting minutes should reflect that there was fairly widespread agreement that INESSS and CADTH assessments are NOT appropriate as reference cases, that the processes in place do not represent a peer-reviewed approach nor are they conducted from a perspective that is appropriate for price setting. Further, as representatives of our industry, we clearly communicated that the HTA cost-utility point estimates will never provide the level of certainty necessary and appropriate for the purposes of price setting within a quasi-judicial context.

We wanted to bring our concerns to your immediate attention and would welcome further discussion and validation of detailed meeting minutes with the working group. To ensure full transparency, we also want this email as well as our email of August 9 to be posted on the BrightShare site so that the Steering Committee members are able to appreciate our views.

We are happy to discuss either of these points if you have any questions, and looking forward to hearing from you to get your perspective on these issues. Thanks.

Geoff and Frederic

Appendix 3.3: Email from Frédéric Lavoie and Geoff Sprang (3/4)

Subject: Next steps for the PMPRB Technical Working Group

Date: 17 August 2018 at 11:17 MST

From: Frédéric Lavoie

To: Mike Paulden

Cc: Edward Burrows, Douglas Clark, Guillaume Couillard, Isabel Jaen Raasch, Matthew Kellison, Nelson Millar, Richard Lemay, Tanya Potashnik, Theresa Morrison, Geoff Sprang, Marie-Claude Aubin, Sylvie Bouchard, Chris Cameron, Christopher McCabe, Donald Husereau, Doug Coyle, Karen Lee, Maureen Smith, Patrick Dufort, Peter Jamieson, Stuart Peacock, Tammy Clifford, Tania Stafinski

Dear Mike,

Firstly, we would like to acknowledge and thank you Mike for the manner in which you have conducted and chaired this working group, maintaining a constructive and professional tone throughout the meetings and calls, despite the widely divergent views of the various group members.

As you and the other working group members know from our repeated reminders, the industry has a fundamental disagreement with the premise of using of the proposed economic factors to establish ceiling prices in the context of the PMPRB's mandate. Chief among those concerns are the difficulties of establishing the so-called "bright lines" which PMPRB itself has identified as an important element of the new regulatory framework, given the inherently subjective nature of point estimates, as well as the technical and operational challenges associated with implementation. These concerns make it very challenging for us to confine our commentary within the very narrow boundaries established by the terms of reference of the Working Group.

Although we have been repeatedly reminded by the PMPRB staff that the mandate of this WG is limited to finding solutions to implement the economic factors proposed in the draft regulations published through the Canada Gazette I process on the assumption that the final regulations published in the Canada Gazette II will be unchanged, we strongly believe it is our responsibility to call attention not only to the issues related to uncertainty and lack of clarity, but also to the significant and, in many cases, insurmountable technical and operational issues associated with the application of these economic factors. We appreciate that many of these issues have also been acknowledged in the perspectives and comments offered by other WG members.

Much if not all of the effort expended by the Working Group in arriving at recommendations will be of limited utility if technical or operational issues render them impossible or impractical to implement. For this reason, we feel strongly that to be informative, the group's recommendations need to be accompanied by comprehensive commentary on the known and potential technical and operational complexities of implementation.

In addition to participating in the initial Working Group meeting on July 26th, we have now attended all of the 8 hours of conference calls scheduled on August 22 and 24, 2018. It would have been helpful to hear from key stakeholders, such as CADTH staff, who were unfortunately not present during these calls. Through all of these discussions what is consistently apparent to us is that there is little if any consensus around the use of economic factors beyond using a set of international pricing reference tests in the regulatory ceiling price-setting exercise.

Despite the many hours of discussion, it appears that the application of the economic factors proposed by PMPRB to the working group remains associated with a lack of clarity. We have heard that this lack of clarity can be accommodated and may in fact provide a desired level of flexibility where economic factors are applied at the level of budget holders to guide decision making. However, in the context of their application in a prescriptive manner to establish an explicit ceiling price, given PMPRB's role as a price ceiling regulator, such a lack of clarity constitutes a critical limitation. Our working group discussions to date have only served to heighten our concerns that the uncertainty associated with their use and interpretation is significant and will not provide a bright line conducive to innovative companies understanding the implications of engaging within the Canadian market the significant resources required to commercialize innovations.

While we are cognizant of the limited terms of reference for this working group prescribed by the PMPRB, we feel it is our responsibility to reiterate to policy makers our strong recommendation that the working assumptions of the WG be revisited and that the Government of Canada urgently establish discussions with our industry to consider alternative regulatory approaches excluding the use of economic factors.

Below are our observations from the working group discussions about each of the six topics in scope that support the above industry perspective:

DRUGS IN CATEGORY 1:

- The industry is favourable to a risk-based approach to PMPRB's regulations; one that is commensurate to the risk of abuse of a patentee's monopoly power. However, this risk categorization cannot be the gate towards the implementation of economic factor adjustments as currently intended in the current draft regulations (use of pharmacoeconomic price tests).
- The initial intent published by PMPRB that categorization of risks is framed on the basis of products having a cost-utility point estimate greater than \$30,000/QALY (corresponds to a supply side estimate of UK willingness to pay threshold) would capture >90% of current patented medicines in Canada.
- The technical difficulty in establishing a cost-utility estimate for a newly launched medicine led the WG to discourage PMPRB for using this as a criterion to define risk.
- The WG thought that this exercise should exclusively include treatment cost per year, market size and degree of innovative value (breakthrough product).
- Preliminary data on risk-based categorization were only verbally shared with the WG by PMPRB staff. Further details and discussion is required before any conclusions could be made.
- The sensitivity of these criteria also needs to be evaluated post application of the first price test of international price referencing. This was not accounted for by PMPRB during its preliminary analyses.

SUPPLY-SIDE THRESHOLD:

- Industry representatives have repeatedly pointed out that the lack of precision (high levels of uncertainty) associated with cost-effectiveness estimates and thresholds of willingness to pay makes the use of these tools inappropriate for price ceiling determinations. This concern has been echoed by patient and HTA representatives. There does appear to be consensus that cost-effectiveness estimates and willingness to pay thresholds are (and should continue to be) used by payers to guide the allocation of limited resources within the preview of budget holders (public and private payers).
- The debates of the WG highlighted that there are various quantitative methods (supply-side and demand-side) that would yield differing estimates of willingness to pay of Canadians all susceptible to uncertainty and therefore open to be debated by stakeholders. Such a subjective estimate is not an appropriate tool to use in a quasi-judicial price ceiling setting exercise.

There was general agreement within the WG that PMPRB's initial position on UK supply-side estimate (\$30,000/QALY) was not appropriate and some academic members of the WG suggested more Canadian specific research would need to be conducted before application in this setting and that status quo be observed until conclusion of Canadian research in this area (pause on the application of the economic factors).

- Another area of contention was raised in the WG deliberations as there is misalignment between the suggestions of PMPRB staff to use a supply side estimate of the Canadian willingness to pay threshold while the mandate of PMPRB is to protect the interests of Canadian consumers, aligning with a demand-side willingness to pay threshold quantitative method. Beside this unresolved issue, the use of demand-side thresholds could necessitate that the PMPRB run as many studies to establish thresholds as there are budget holders within the fragmented Canadian pharmaceutical system. Variability across multiple thresholds will also likely raise questions amongst patient stakeholders as to why certain areas and/or diseases are confronted to a lower threshold than other areas and/or diseases. There are many such ethical questions that have not been studied as part of Health Canada and the PMPRB's proposals.
- The uncertain nature of any cost-effectiveness threshold would represent an unrealistic reference for an innovative patented pharmaceutical tested against its equally uncertain cost-utility value.

MARKET SIZE:

- Mitigating the risk of budget impact is an objective of public and private payers in Canada. These stakeholders have effective tools to address the perceived risk pertaining to the anticipated market size a medicine would detain.
- It was acknowledged that use of a gross (or even net) sales number to make ceiling price adjustments ignores the actual budget impact which is more important to payers and which is also a more appropriate consideration in terms of rewarding innovation and influencing the allocation of resources. However, there is no practical or effective way to actually prospectively define this factor and any methodology used to forecast this factor would be accompanied by enormous uncertainty. It is also important to note that such factors are already routinely addressed at the level of budget holders through product listing agreements.
- Establishing a price ceiling threshold based on GDP factors is also problematic given economic variability and more importantly differences across jurisdictions and payer segments in definitions of affordability as well as local or regional healthcare priorities. Affordability and healthcare priorities are ultimately policy decisions best left with

individual jurisdictions. Such considerations are already addressed via existing government mechanisms (e.g. pCPA)

- Notwithstanding the industry opposing position, if pharmacoeconomic factors were implemented, why would patentees need to have their prices adjusted further for market size if they are delivering more value for money as use increases? Operationally, when does this adjustment happen?

MULTIPLE INDICATIONS:

- The uncertainty associated with potential in-market price adjustments resulting from the introduction of new indications or changes in the mix of business resulting from changes in medical practice or competitive dynamics would discourage manufacturers from launching new indications and make it more difficult to make launch decisions for Canada, thereby resulting in delays or potentially loss of access to innovative medicines.
- The practical limitations of tracking and reporting by indication make implementation effectively impossible in the context of the current Canadian prescription drug setting.
- Even in a hypothetical context when a subsequent indication of an already approved medicine would be associated with a higher cost-utility, there is no mechanism in place to implement differential pricing on a per indication basis. Furthermore, the behaviour of payers in reimbursement negotiation appears to follow a price-volume rationale over medicines' life cycle.

PERSPECTIVE:

- The societal perspective is the broadest perspective theoretically speaking but it is associated with important technical measurement hurdles. In a societal perspective, the evaluation of indirect costs has been the subject of important equity issues due to their discriminatory nature. The valuation of productivity through indirect costs often yields to the prioritization of treatments predominantly destined to working age Canadians at the expense of those targeting an older population more likely retired from the work force.
- Again, the expression of a bright line for price ceiling setting of pharmaceuticals would be blurred as a result of the lack of clear consensus in the academic community on which perspective is best, how to measure it adequately and how to shelter it against the accusation of it leading to discriminatory practices. These issues will make it difficult for the WG to come up with a meaningful recommendation.

ACCOUNTING FOR UNCERTAINTY:

- Regulating ceiling prices on the basis of factors that would be measured through payer processes not intended for price setting are a cause for concern. This was raised by the WG during the discussion on uncertainty.
- CADTH and/or INESSS that would produce cost-utility point estimates for medicines in Canada often exhibit differences in their estimates pertaining to heterogeneous assumptions and expert opinions. Their processes do not incorporate state of the art validation steps and levels of peer-reviews.
- The WG discussed the option of creating a new health economics committee to provide enhanced rigour in the evaluation. However, it was noted that the important shortage of trained health economist experts in Canada would make the composition of such group difficult and duplicative. This would also add another layer of complexity and delays on the already difficult Canadian journey of a pharmaceutical innovation.

The compounded uncertainty across multiple proposed economic factors is contrary to the PMPRB's stated objective of providing innovators with a bright line in forecasting ceiling prices of innovative entrants in the Canadian market.

As the working group moves to the next steps, it will be helpful to get clarity on the process for developing recommendations and the role of the PMPRB Steering Committee (SC) in this regard. We have been informed that the PMPRB staff clarified at the last SC meeting that the role of the SC is not to steer the work of the working group. This raises a serious governance and procedural question regarding the next steps in the process of development of any recommendations through the working group and the role of the SC in approving the recommendations.

Thanks in advance for the work you will do to fully integrate the above considerations into the WG's outputs.

Sincerely,

Frederic & Geoff

Appendix 3.4: Email from Frédéric Lavoie and Geoff Sprang (4/4)

Subject: Feedback related to September 25 meeting

Date: 3 October 2018 at 13:55 MST

From: Frédéric Lavoie

To: Mike Paulden

Cc: Geoff Sprang, Marie-Claude Aubin, Sylvie Bouchard, Christopher McCabe, Donald Husereau, Doug Coyle, Karen Lee, Maureen Smith, Patrick Dufort, Chris Cameron, Peter Jamieson, Stuart Peacock, Tammy Clifford, Tania Stafinski, Edward Burrows, Douglas Clark, Guillaume Couillard, Isabel Jaen Raasch, Matthew Kellison, Nelson Millar, Richard Lemay, Tanya Potashnik, Theresa Morrison

Dear Mike,

In follow up to our Technical Working Group call on September 25th, and as the representatives of the industry subject to the PMPRB's guidelines, we wanted to capture and convey to you our key takeaways from the discussion as well as our understanding of next steps.

Once again, we want to commend you for your thoughtful and inclusive approach to a complex and challenging process given the limiting terms of reference set by PMPRB for the Working Group and diversity of views represented in the group. While we have provided some additional commentary specific to the six pre-specified areas below, it was apparent to us that we are still struggling to arrive at a consensus in any of these six areas and we appreciate your candor in acknowledging this at the close of the meeting. As we have stated repeatedly, the heterogeneity of opinions within the working group and the inability of the group to forge a consensus when it comes to the application of economic factors to price regulation is illustrative of the issues that form the basis of the regulated industry's concerns; specifically the degree of uncertainty, the lack of "bright lines" and the complexity of implementation which in our view represent critical limitations of the proposed regulatory framework.

We understand that the proposed next steps are the circulation of a draft report by October 5th for review by members prior to a final meeting of the Working Group on October 12th at which voting on the final recommendations will take place. Materials provided to you in advance of October 5th may be incorporated into the draft report. However, those provided after issuance of the draft report may still be considered at the October 12th meeting. The Final Recommendations of the Working Group will be issued at some point shortly thereafter to the Steering Committee for consideration in late October. However, the Steering Committee will not see any draft materials or commentary from the Working Group. Given the complexity of the

issues, we believe that the Working Group does not have sufficient time to complete its work in the timeframe defined by PMPRB.

Given that the Working Group's Terms of Reference state that recommendations will be determined by a simple majority vote, and in view of our comments above, we anticipate that arriving at a single set of coherent recommendations that "do justice" to the complexity of the issues will be extremely challenging and that what is ultimately presented to the Steering Committee may fail to reflect the underlying heterogeneity of opinion. Under these circumstances, we believe it is critical that the questions that will be subject to a vote, the process by which all of the results will be captured and reported, as well as the content and format of what will be shared with the Steering Committee and other relevant stakeholders be well defined in advance. We would therefore ask that these considerations be drafted and shared with the Working Group as soon as possible and before the voting process is launched. The Working Group members should be allowed to comment on the proposed process prior to undertaking any voting. We take comfort with your commitment of filing in the appendix of the final report the written comments of the Working Group members who wish them to be "on record". As such, please consider this email "on record".

In addition, and for reasons outlined previously, we believe that it will be important for stakeholders reviewing the output of the Working Group to be provided with information relating to the technical feasibility and other implementation issues and challenges associated with recommendations. It was our understanding from discussions at the September 12th meeting that PMPRB staff were to provide case studies to inform the Working Group's deliberations and we are disappointed that they have not done so to date. The suggestion from PMPRB staff that Working Group members with expertise and examples may bring these forward has come in the final weeks of the group's deliberations and provides an insufficient opportunity for their development and consideration. As industry representatives, and although we believe that it should be the responsibility of PMPRB staff as opposed to Working Group members to provide case studies, we will attempt to compile some case studies to share with the group in advance of our next meeting.

With respect to the six specific areas for consideration, as noted previously we do not support the inclusion of economic factors in a quasi-judicial price ceiling regulatory methodology given the uncertainty these would introduce, the practical challenges and complexity of implementation and the fact that the government's regulatory objectives can be achieved by much simpler, more transparent and predictable mechanisms. Our observations of the group's discussion are provided below.

1. Perspective – while some members expressed the view that a health system perspective would be preferable to a societal perspective in order to minimize discriminatory bias (e.g. productivity considerations), other members raised the concern that the health system perspective fails to account for the private for-profit

segment of the market. The concern that private payers are “profit-maximizers” and that potential price reductions may not be passed on to consumers has also been raised.

2. Threshold – there were differing points of view on whether the thresholds should be determined by supply side or demand side considerations. There was also a view that PMPRB cannot “enforce” or regulate efficiency and WTP varies, so it may be better to set an upper limit on all but let payers negotiate. There was some support for additional empirical work as general agreement that thresholds used in existing HTA assessments would not appropriately reflect collective WTP. The need for further research in this area in which current empirical work is insufficiently mature and not Canada specific has also been raised.
3. Uncertainty – Uncertainty is reflected in HTAs and resulting decision making by considering the range of possible ICERs rather than a point estimate. HTAs are not performed with the objective of determining a point estimate for price setting. New drugs are introduced and priced at the point of maximum uncertainty which typically declines over time.
4. Market Size – recognition of the fact that net budget impact is more important than gross sales; challenges in defining this ex ante given uncertainty in forecasting.
5. Multiple Indications – general agreement that pricing by indication is theoretically appealing, it is not possible given current limitations in data capture and reporting. Practically it seems necessary to regulate one price across indications, however there was no agreement on how a single price across indications would be established.
6. Category 1 Criteria – general agreement that CE would not be appropriate screening criteria, support for risk based approach, some support for use of level of therapeutic improvement and new MOA as a consideration, concerns expressed about market size vs net budget impact as this could distort screening, also concerns expressed about impact of a specific threshold on orphan drugs.

We look forward to your response. If you have any questions, please do not hesitate to contact us.

Regards,

Geoff and Frederic

Appendix 3.5: Summary comments from Frédéric Lavoie and Geoff Sprang

Date: 1 March 2019 at 15:00 MST

As members of the Technical Working Group (TWG) representing BIOTECanada and Innovative Medicines Canada, we wish to enter the following summary of observations and issues into the record on behalf of our respective memberships, who represent most of the patentees subject to the PMPRB's jurisdiction.

As both organizations have previously communicated, we believe the use of the proposed economic factors in the context of quasi judicial price regulation is inappropriate. Our concerns in this regard and the underlying rationale have been captured elsewhere and for that reason are not restated here but can be reviewed under on the record comments in the appendix of the TWG report. However, our participation in the TWG and the opportunity to further explore the complex issues associated with the use of economic factors in this way has only served to reinforce our concerns that these reforms will, at best, delay access to new therapeutic options for Canadian patients, and potentially impede access altogether to the extent that manufacturers elect not to launch new therapeutic products in Canada.

Overall, a key concern was lack of clarity around the overarching policy objectives. In a number of cases the TWG was unable to arrive at clear recommendations and ultimately determined that the questions posed could only be answered with further clarification of PMPRB's policy objectives. The fact that such objectives were not sufficiently clear to the TWG is in and of itself problematic and limited the value of the TWG. We also note that the deferral within the proposed recommendations to "policy intent" should not be construed as support for the proposed new economic factors.

Another important and challenging topic for TWG consideration was Topic 5 – Perspective which, under the Terms of Reference, required the TWG to discuss options to account for the consideration of a public health care system versus a societal perspective. Given the heterogeneous nature of the Canadian payor landscape, which includes public payors, employer-sponsored privately funded plans as well as cash paying customers, discussions of this topic reflected very divergent views. It is disappointing and, in our view, inappropriate that, having asked the TWG to provide advice, the PMPRB intervened and imposed the decision to adopt a public health care system perspective without regard to the diverse views of the expert members of the TWG.

In addition, we believe that the Terms of Reference for the TWG greatly limited the value of the exercise in leveraging both the practical and academic expertise of the members. For example,

we feel it is important to register our concern and disappointment that important feasibility issues related to implementation were considered out of scope; particularly as the TWG is the only forum specifically charged with consideration of technical questions related to implementation. We find it inconceivable that the proposed regulatory reform process has reached this stage without having given due consideration to technical feasibility.

Our efforts to call out significant feasibility challenges were essentially dismissed by PMPRB staff. In some cases the feasibility issues that we attempted to raise are substantive enough that patentees subject to the proposed regulation changes do not currently have the ability to comply with the new reporting requirements. In other cases, our compliance with the proposed reforms would have major implications for resourcing and enterprise system reconfiguration adding enormously to the existing cost and regulatory burden of reporting by patentees. Significantly adding to the regulatory burden without due consideration to alternative regulatory options makes no sense and runs counter to the federal government's efforts to reduce so-called "red-tape".

We also want to register our concern that despite numerous requests and emphasis on the need for case studies to be developed to explore how the proposed reforms would be applied, case studies were only made available in the final stage of the TWG deliberations and a review and discussion of all 6 individual case studies was allocated only 35 minutes on the agenda of the one meeting where they were discussed. A robust discussion of these case studies would have added greatly to the TWG's deliberations. The case studies themselves, which were developed by the PMPRB, raise numerous issues that are illustrative of the kinds of challenges that will arise if the current regulatory revisions are implemented as proposed. It is noteworthy that despite significant efforts within our respective trade associations as well as the use of external pricing and analytical expertise, we were unable to reverse engineer or replicate the PMPRB's results. This is concerning in and of itself and underscores the need for additional consultation. The magnitude of price reductions illustrated by the case studies also raises concerns since it is clearly not aligned with the Regulatory Impact Analysis Statement and Cost-Benefit Analysis released by Health Canada with the draft regulatory amendments or with the objective of aligning Canadian prescription drug prices with those of a broader subset of reference markets. When these issues were raised at the TWG they were not adequately addressed by PMPRB staff.

Overall, while we appreciate the efforts of the Chair (Mike Paulden) to execute the mandate he was given as impartially as possible, the mandate itself (Terms of Reference), the limitations placed on the scope of the TWG's considerations (notably the exclusion of considerations of technical feasibility), the lack of clarity early in the process surrounding the PMPRB's policy intent that limited the TWG's ability to provide meaningful recommendations in many areas, the late availability and insufficient time allocated to the consideration of case studies and the decision of the PMPRB to disregard the TWG's deliberations of Topic 5 (Perspective), combined to render the TWG exercise inadequate as a consultation process.

As representatives of the innovative industry, we have clearly acknowledged the challenges facing governments in meeting the expanding healthcare demands and we reiterate our willingness to work with governments and other stakeholders to find appropriate solutions. These solutions must reflect a comprehensive and balanced policy framework that extends beyond pharmaceutical price ceiling controls to include the objective of ensuring Canadians have timely access to the best treatment options and to preserving Canada's attractiveness as a destination for life sciences research and investment. Therefore, as it relates to price ceiling regulatory reforms, we continue to advocate for more robust consultations with representatives of industry, patient associations, other federal government ministries as well as provincial governments, all of whom share the objective of improving the health and well-being of Canadians.

Appendix 3.6: Summary comments from Maureen Smith

Date: 1 March 2019 at 15:59 MST

As a member of the Technical Working Group, I would like the following comments to be included in the appendices of the Technical Working Group (WG) Final Report. When I accepted the invitation to join the PMPRB's Technical Working Group in July 2018, I knew that it would be challenging to provide my own patient perspective in a Working Group whose purpose was to inform the PMPRB Steering Committee on the modernization of price review process guidelines. After all, not many patients know about this quasi-judicial body that sets price ceilings for patented drugs in Canada, yet these ceiling prices are important to patients as they can have consequences on the sustainability of our health care system and access to medications. I have spent the past five years as a patient member of a provincial health technology assessment body, therefore, I felt that I had enough understanding of health economics to participate in the discussions and hopefully bring my lived experience as a Canadian with a rare disease who relies on drugs and has dealt with access issues.

Unfortunately, I believe that the WG was not able to engage in a discussion that would have allowed us to deliver on our terms of reference. Simply put, the terms of reference were not reflective of the scope of the Technical WG. Much of what we were tasked to discuss in the six areas of focus was pre-determined by the Regulatory Impact Analysis Statement (RIAS) that were published in the Canada Gazette, Part 1. For example, after two months of discussion on the options to account for the consideration of a public health care system versus societal perspective, the WG was informed by the PMPRB that, as stated in the RIAS, they were adopting a public health care system perspective. Why then was the WG ever asked to discuss perspective? Given that we do not have a national pharmacare program in Canada and that Canadian consumers use public plans, private insurance, or pay out of pocket for their drugs, it was disappointing that the perspective had already been determined.

The WG was told that other topics were out of scope as well, despite a terms of reference that suggested otherwise. While I appreciate that we were not there to debate the RIAS, the terms of reference should have been more aligned with the RIAS and its constraints. Another barrier to fulfilling our mandate was the lack of a proper review of empirical evidence on each topic. This should have been undertaken, rather than relying on WG members' own knowledge of what was available and personal biases. Finally, as early as the first meeting and then repeatedly several WG members requested that the PMPRB develop case studies that would allow us to work through the technical details and have a better understanding of the impact. Case studies that were developed for the Steering Committee were finally made available to us and we were granted 30 minutes to discuss this during our final meeting.

The recommendations you see will most likely have a high degree of agreement because, except for a few, they cannot truly be considered recommendations if one looks at the specific questions in our six areas of focus. They are a record of whether the members of the WG agree on our conclusions. There really isn't much to disagree on, since no resources were invested in synthesizing the existing empirical evidence, resulting in little space for a thoughtful technical discussion. As I see it, the WG's recommendations fall into five categories: (1) advising the PMPRB to adopt measures that will be consistent with their policy intent; (2) recommendations that simply state that this is the only option because of the policy intent; (3) those that deal with the enormous challenges of applying health technology assessment to a country with 17 jurisdictions who each have their own drug budgets and priorities; (4) recommendations that state the WG's conclusions such as 2.3 "The WG regards the direction and magnitude of any bias in the \$30,000 per QALY estimate by Ochalek et al. (2018) to be unknown"; and (5) recommendations that call on further empirical research. For me, this is the result of 31 hours of discussion and, unfortunately, the impact is minimal due to the failure in the process.

As a patient, my goal was to contribute to the discussion of achieving the fine balance that doesn't discourage market access while charging prices that payers feel will protect the public health system. Patients are concerned about the prices of drugs but they are also concerned about having access to innovative therapies in Canada. There is some evidence that countries such as Australia and New Zealand who have some of the toughest drug prices have less access. Another concern is whether the application of health technology assessment tools by the PMPRB will result in further inequity in access to drugs for Canadians, especially for those relying on drugs for rare diseases whose coverage is often determined by their postal code. Will they acknowledge the challenges of HTA for rare disease drugs, especially the inappropriateness of thresholds? Finally, if the PMPRB expands its mandate to integrate HTA into setting ceiling prices, they should have a process for patient input into their work similar to the patient submission processes that our Canadian HTA agencies have adopted.

In conclusion, it is my opinion that the PMPRB missed an opportunity to truly consult the WG members as much of the outcome was pre-determined by the key guideline document (the RIAS) and there was a lack of clarity on the policy intent from the outset. It is worrisome that the Technical WG was not able to debate the important considerations and reduce some of the uncertainty in what the consequences will be for Canadian patients by making recommendations that would have reflected our best thinking.

Appendix 4: Terms of Reference



Terms of Reference for Working Group to Inform the Patented Medicine Prices Review Board (PMPRB) Steering Committee on Modernization of Price Review Process Guidelines

Background

The Patented Medicine Prices Review Board (PMPRB) recently established a 'Steering Committee on Modernization of Price Review Process Guidelines'. The mandate of this **Steering Committee** is to assist the PMPRB in synthesizing stakeholder views on key technical and operational modalities of the PMPRB's new draft Guidelines.

The Steering Committee's work will be based in part on the analysis and recommendations of a technical **Working Group**, which will examine certain issues that the Steering Committee believes would benefit from the review of experts in health technology assessment and other economic and scientific matters.

The Working Group will comprise leading experts in pharmacoeconomics and the clinical evaluation of pharmaceuticals. The Working Group will meet twice in-person and multiple times via tele-conference between July and October 2018. A report of the Working Group's deliberations and recommendations will be produced by the chair and submitted to the Steering Committee for consideration in October 2018.

Membership

The chair of the Working Group will be Dr Mike Paulden (University of Alberta).

Thirteen individuals will sit as members of the Working Group (listed alphabetically):

1. Sylvie Bouchard (Patrick Dufort as alternate if needed) (INESSS);
2. Dr Chris Cameron (Dalhousie University and Cornerstone Research Group);
3. Dr Tammy Clifford (University of Ottawa and CADTH);
4. Dr Doug Coyle (University of Ottawa);
5. Don Husereau (University of Ottawa);
6. Dr Peter Jamieson (University of Calgary);
7. Dr Frédérick Lavoie (Pfizer Canada);
8. Dr Karen Lee (University of Ottawa and CADTH);
9. Dr Christopher McCabe (University of Alberta and Institute of Health Economics);
10. Dr Stuart Peacock (Simon Fraser University and BC Cancer Agency);
11. Maureen Smith (Patient);
12. Geoff Sprang (Agmen);
13. Dr Tania Stafinski (University of Alberta).

Two individuals will sit as observers of the Working Group:

1. Edward Burrows (Innovation, Science and Economic Development);
2. Nelson Millar (Health Canada).

One individual will act as an external reviewer of the Working Group's draft report:

1. Dr Mark Sculpher (University of York).

Recommendations of the Working Group will be determined by a vote of the members. In the event of a tie, the chair will have the casting vote.

Areas of focus

The Working Group will examine and make recommendations with respect to the following considerations and questions:

1. Options for determining what medicines fall into 'Category 1'

- A Category 1 medicine is one for which a preliminary review of the available clinical, pharmacoeconomic, market impact, treatment cost and other relevant data would suggest is at elevated risk of excessive pricing.
- The following criteria have been identified as supporting a Category 1 classification:
 - a) The medicine is 'first in class' or a 'substantial' improvement over existing options
 - b) The medicine's opportunity cost exceeds its expected health gain
 - c) The medicine is expected to have a high market impact
 - d) The medicine has a high average annual treatment cost
- Should other criteria be considered? What are the relevant metrics for selecting medicines that meet the identified criteria and what options exist for using these metrics?

2. Application of supply-side cost effectiveness thresholds in setting ceiling prices for Category 1 medicines

- Potential approaches for implementing a price ceiling based on a medicine's opportunity cost.
- Potential approaches for allowing price ceilings above opportunity cost for certain types of medicines (e.g. pediatric, rare, oncology, etc)

3. Medicines with multiple indications

- Options for addressing medicines with multiple indications (e.g. multiple price ceilings or a single ceiling reflecting one particular indication).

4. Accounting for uncertainty

- Options for using the CADTH and/or INESS reference case analyses to set a ceiling price.
- Options for accounting for and/or addressing uncertainty in the point estimate for each value-based price ceiling.

5. Perspectives

- Options to account for the consideration of a public health care system vs societal perspective, including the option of applying a higher value-based price ceiling in cases where there is a 'significant' difference between price ceilings under each perspective.
- How to define a 'significant' difference in price ceilings between each perspective.

6. Application of the market size factor in setting ceiling prices

- Approaches to derive an appropriate affordability adjustment to a medicine's ceiling price based on an application of the market size and GDP factors (e.g. based on the US 'ICER' approach).

Additional areas of focus may be identified by the Steering Committee prior to the first meeting of the Working Group in July 2018.

It is anticipated that the approaches or methods recommended by the Working Group may not be identical to approaches or methods currently employed by CADTH or INESSS. Where such departures present potential hurdles for operationalization of its recommendations, the Working Group will identify potential technical or other solutions to these hurdles.

Confidentiality

Working Group members may consult with non-members on an ongoing basis but are expected to maintain the confidentiality of any materials provided to them during the course of their work.

The names of the members of the Working Group will be published on the PMPRB's website, along with a report of its deliberations, analysis and recommendations.

Governance and procedure

It is recognized that members of the Working Group may hold opposing points of view on the above issues and/or disagree with the policy rationale underlying the changes to the PMPRB's Guidelines. Members are nonetheless encouraged to work together constructively to assist the Working Group in carrying out its function.

The chair is expected to foster consensus among members, but in order to ensure that Working Group deliberations are as focused and productive as possible, the chair shall have final say on all matters of governance and procedure. Members who disagree with a decision of the chair in this regard can request that their objection be noted on the record. The chair shall make every

effort to ensure that the Working Group's final report accurately reflects any important points of convergence or contention between members.

Schedule

The Working Group will meet for the first time in-person in Ottawa in July, followed by numerous tele-conferences in August and September. Following submission of a draft report, a second in-person meeting will be held in October.

All dates are subject to the availability of the chair and members of the Working Group.

Date	Event	Purpose
26 July 2018	Full day in-person meeting in Ottawa	Overview of Working Group objectives. Summary of specific areas of focus under consideration. Allocation of tasks among Working Group members.
22-24 August 2018	One-hour teleconference on each area of focus	Opportunity for input from Working Group members.
24 August 2018	Two-hour tele-conference	Update on Working Group status. Opportunity for input from Working Group members.
Week of 10 September or 24 September 2018 (TBC)	Two-hour tele-conference	Update on Working Group status. Opportunity for input from Working Group members.
5 October 2018	Draft report circulated among PMPRB staff and Working Group members	Opportunity for input from PMPRB and Working Group members.
12 October 2018	Full day in-person meeting in Ottawa	Present draft report. Report draft recommendations. Final opportunity for input from PMPRB and Working Group members.
26 October 2018	Final report delivered to PMPRB	Final deliverable to PMPRB.

Deliverables

A draft report will be circulated among PMPRB staff and Working Group members on 5 October 2018, prior to the final in-person meeting in Ottawa. A final report will be submitted to the PMPRB on 26 October 2018 and circulated among Working Group and Steering Committee members.

Following delivery of the final report, the chair will be willing to present the recommendations of the Working Group to stakeholders and other interested parties, subject to availability.

Budget

The PMPRB may cover reasonable travel and accommodation costs of members where such funding is requested and approved in advance. Where possible, the chair of the Working Group will arrange meetings to attempt to minimize expenditures for participants.

Appendix 5: Policy Intent

Appendix 5.1: Regulations Amending the Patented Medicines Regulations



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- [December 2, 2017 \(/rp-pr/p1/2017/2017-12-02/html/index-eng.html\)](/rp-pr/p1/2017/2017-12-02/html/index-eng.html)

Vol. 151, No. 48 — December 2, 2017

Regulations Amending the Patented Medicines Regulations

Statutory authority

Patent Act

Sponsoring department

Department of Health

REGULATORY IMPACT ANALYSIS STATEMENT

(This statement is not part of the Regulations.)

Executive summary

Issues: The Patented Medicine Prices Review Board (“PMPRB” or “the Board”) uses a regulatory framework that currently falls short of its mandate to protect Canadian consumers from excessive prices for patented medicines. Canada’s patented medicine prices are among the highest in the world, and despite significant changes in the medicine market, the *Patented Medicines Regulations* have not been substantively changed in over two decades. The Regulations need to be modernized to provide the PMPRB with more relevant and effective regulatory tools in order to better protect Canadians from excessive prices for patented medicines.

Description: This proposal would amend the *Patented Medicines Regulations* (“Regulations”) so that the PMPRB’s regulatory framework includes new price regulatory factors and patentee price information reporting requirements that will help the PMPRB to protect Canadian consumers from excessive prices. There are five elements.

New price regulatory factors and updating the schedule of comparator countries

(1) Providing the PMPRB with three new price regulatory factors to enable it to consider the price of a patented medicine in relation to its value to patients and impact on the health care system.

(2) Updating the schedule to the Regulations that sets out the countries (now the PMPRB7) on which patentees report pricing information to include countries with similar consumer protection priorities, economic wealth, and marketed medicines as Canada. This would provide the PMPRB with the information needed to regulate prices based on comparisons that are more closely aligned with the PMPRB's mandate and Canada's domestic policy priorities.

New reporting requirements

(3) Reducing reporting obligations for patented veterinary, over-the-counter and "generic" medicines (i.e. those authorized for sale by the Minister of Health through an Abbreviated New Drug Submission [ANDS]). As these products pose a lower risk of asserting market power and charging excessive prices, this reduction would enable the PMPRB to focus on medicines at higher risk of excessive pricing.

(4) Amending patentee price information reporting requirements to include reporting in relation to the new factors.

(5) Requiring patentees to report price and revenue information net of all price adjustments such as direct or indirect third party discounts or rebates. This would ensure that the PMPRB is fully informed of the actual prices for patented medicines in Canada and enhance the relevance and impact of domestic price comparisons.

Cost-benefit statement: The proposed amendments would produce an estimated net benefit to Canadians of \$12.6 billion net present value (NPV) over 10 years due to reduced prices for patented medicines. Lower prices would alleviate financial pressures on public and private insurers and improve affordable access for Canadians paying out-of-pocket. Lost revenues to industry are estimated to be \$8.6 billion present value over 10 years. Costs to industry are estimated to be \$9K/year in total, including administrative and compliance costs. Government costs of approximately \$8.8M/year (PV) would include increasing the PMPRB's staff and resources for an anticipated increase in compliance and enforcement activities.

It is not anticipated that these amendments would generate adverse impacts on industry employment or investment in the Canadian economy. Although when the current regulatory framework was first conceived 30 years ago, policy makers believed that patent protection and price were key drivers of medicine research and development (R&D) investment, there is no evidence of this link. The level of industry R&D investment relative to sales by medicine patentees in Canada has been falling since the late 1990s and is now at a historic low despite Canada having among the highest patented medicine prices in the world. These amendments would aim to align Canadian prices with those in countries that, despite having lower prices, receive higher medicine industry investment.

"One-for-One" Rule and small business lens: The "One-for-One" Rule applies and the anticipated administrative burden is estimated to be \$3,062 (2012 dollars) annually. The small business lens does not apply.

Domestic and international coordination and cooperation: Price regulations on medicines are a common international practice, although there is a significant variation in approach. These differences often arise from a need to tailor policy instruments to work within each

country's health care system. While countries monitor foreign models, it is to keep abreast of international best practices, rather than to harmonize. Regulating the prices for patented medicines to be non-excessive is not subject to trade provisions.

Background

Patented medicines are an important part of Canada's health care system

Patented medicines help prevent and cure disease as well as save lives. But Canadians are not getting the value for money on prescription medicine spending or the outcomes they deserve. Medicine spending in Canada has increased from less than 10% of total health expenditure, when Medicare was first established 49 years ago, to about 16% today. Medicines are now the second-largest category of spending in health care, ahead of physician services and behind total hospital spending (which includes medicines used in hospital). Canadians are spending more per capita on medicines than any other country in the world, with the exception of the United States. Greater medicine expenditures can limit access to innovative medicines by straining the budget envelope for medicines of public and private insurers, place a financial burden on patients who pay out of pocket for their medicines, and mean fewer resources for other critical areas of the health care system.

In January 2016, federal, provincial and territorial ministers agreed to work together to improve the accessibility, affordability, and appropriate use of medicines to better meet health care system needs. The Government of Canada is committed to this work and is taking action to lower the cost of medicines, provide faster access to new medicines that are safe and effective, and support the development of tools for more appropriate prescribing. To support these actions, Budget 2017 outlined an investment of \$140.3 million over five years, starting in 2017–2018, and \$18.2 million, for ongoing years. The proposed regulatory amendments contribute to this initiative with respect to the price of patented medicines.

The Patented Medicine Prices Review Board ("PMPRB" or "the Board")

The PMPRB was created in 1987 as the consumer protection "pillar" of a major set of reforms to the *Patent Act* ("Act"), which were designed to encourage greater investment in medicine R&D in Canada through stronger patent protection. The Act sets out the period of time that patentees of a medicine are provided the exclusive rights granted by a patent. It also establishes the PMPRB as a quasi-judicial body with a price regulatory mandate to ensure that patentees do not abuse their patent rights by charging consumers excessive prices during this statutory monopoly period.

The Act and the *Patented Medicines Regulations* ("Regulations") together form the patented medicines price regulatory framework of the PMPRB. Regulations with respect to patented medicine prices and information are made pursuant to the Minister's recommendation; however, the PMPRB carries out its regulatory mandate at arm's length from the Minister.

The Patent Act and Patented Medicines Regulations

Although no definition of "excessive" is included in the regulatory framework, it does specify the factors and information that the Board must consider in determining whether a price is excessive. The current price regulatory factors as set out in section 85 of the Act are the following:

- The prices at which the same medicine has been sold in the relevant market;

- The prices at which other medicines in the same therapeutic class have been sold in the relevant market;
- The prices at which the medicine and other medicines in the same therapeutic class have been sold in countries other than Canada; and
- Changes in the Consumer Price Index.

The Regulations specify the price information that patentees must report to the PMPRB to allow it to regulate prices and report on trends. They include requirements to report the identity and price information for patented medicines sold in Canada and their prices in seven foreign countries where they are also sold. Currently the seven countries set out in the schedule to the Regulations (the PMPRB7) are the United States, the United Kingdom, France, Germany, Switzerland, Italy and Sweden. Although section 85 of the Act allows for further price regulatory factors to be prescribed in the Regulations, none have been proposed for consideration until now.

The PMPRB's Compendium of Policies, Guidelines and Procedures

Many of the core regulatory concepts in the Act and the Regulations have been further developed in, and are operationalized through, guidelines. The PMPRB is authorized to make non-binding guidelines under section 96 of the Act, subject to consultation with relevant stakeholders. The purpose of the guidelines is to establish, and ensure that patentees are generally aware of, the policies and procedures undertaken by the Board staff to identify the medicines that might be priced excessively.

How the current regulatory framework works

Under the PMPRB's current regulatory framework, as operationalized through the guidelines, new patented medicines are assessed for the degree of therapeutic benefit they provide relative to existing medicines on the market. Depending on the outcome of that process, the PMPRB determines a price ceiling for new patented medicines that is based either on the median price of that same medicine in the PMPRB7 countries, the highest-priced medicine in Canada in the same therapeutic class, or some combination of the two. Once a patentee sets a medicine's introductory price in relation to that ceiling and it enters the market, the PMPRB allows annual price increases in keeping with the Consumer Price Index (CPI), provided these increases do not make the Canadian price greater than the highest price of the same medicine among the PMPRB7 countries.

The PMPRB's current regulatory framework is operationalized by Board staff who investigate medicines that appear to be priced excessively. Board staff apply the tests and thresholds specified in the guidelines to each patented medicine sold in Canada, notify the patentee that they are under investigation if the prices fail those tests and thresholds, and try to negotiate a voluntary compliance undertaking (VCU) by the patentee based on the compliant price level as set out in the guidelines. A VCU is a written commitment by a patentee to comply with the PMPRB's guidelines, including adjusting the price of the patented medicine in question to a level that complies with the guidelines and offsetting any potential excess revenues that may have been received as the result of having sold the patented medicine at a non-guideline compliant price in Canada.

If an acceptable VCU is not concluded, the case proceeds to a public adversarial hearing in front of a panel composed of members of the Board. During a hearing, the Board panel acts as a neutral arbiter between the parties (Board staff and the patentee). The Board panel must consider every factor under subsection 85(1) in determining whether the price of a medicine sold in Canada is excessive. The Board panel is not

bound by the guidelines during a hearing, although the Board staff, when presenting evidence in front of the Board, often relies on tests and methods that appear in the guidelines as part of its case that the medicine has been sold at an excessive price. If the Board panel determines that the medicine was sold at an excessive price, it may issue an order to enforce a non-excessive price and order the patentee to repay any excess revenue that resulted from selling the drug at an excessive price. An order of the Board can be enforced in the same manner as an order of the Federal Court.

Canada's changing market and rising medicine costs

Since the establishment of the PMPRB three decades ago, the medicine market has changed significantly. Medicine development is increasingly focussed on higher-cost medicines, such as biologics, genetic therapies targeted to smaller patient populations and medicines for rare diseases. The risk of asserting market power through excessive pricing is often greater for these products since there are few, if any, substitutes, and the patentee is not subject to competition. This is especially true for medicines that are first of their kind, or for which alternatives are less effective or have less tolerable side effects.

The current market dynamic has contributed to a significant increase in the cost of medicine in Canada which, if left unaddressed, is expected to continue. Between 2005 and 2016, the number of medicines in Canada with annual per-patient treatment costs of at least \$10,000 increased from 20 to 135. This represents between 30% and 40% of new patented medicines coming under the PMPRB's jurisdiction each year and is a dramatic increase in these types of medicines over a brief timeframe. In 2015, 20 medicines had annual per-patient treatment costs over \$50,000. High-cost specialty medicines now account for nearly one quarter of public and private insurer costs, but less than 1% of their beneficiaries.

Canadian patented medicine prices are among the highest in the world. Of all 35 Organisation for Economic Co-operation and Development (OECD) member countries, only the United States and Mexico have higher patented medicine prices than Canada. In 2015, median OECD prices for patented medicines were on average 22% below those in Canada.

Confidential price adjustments

Medicine manufacturers increasingly negotiate price adjustments with insurers in exchange for having their products reimbursed through insurance plans. These price adjustments are typically negotiated in confidence, with the agreement that they not be disclosed publicly. This means that there is a growing discrepancy between public list prices and lower actual prices paid in the market due to the increased use of confidential price adjustments.

Limitations of current price regulation

For the past 20 years, many countries that set price limits on medicines have relied on international price comparison between countries. With the emergence of higher-cost medicines, coupled with confidential price adjustments, countries have had to modernize with new methods that, for those medicines, are more reliant on assessing the economic value of a new medicine to their respective health systems and less on comparing prices internationally. Between 2010 and 2012, 23 European countries began planning or executed significant reforms to their regulatory frameworks for patented medicine prices. While international price comparison is still widely used in international price regulation, it is increasingly used as an adjunct to other pricing factors.

Price regulatory factors

Section 85 of the Act sets out the price regulatory factors that the Board must consider in determining whether a medicine is being or has been sold at an excessive price in Canada. The current price regulatory factors direct the Board to consider the prices at which a medicine or other medicines in the same therapeutic class have been sold in other countries. The PMPRB relies upon public prices when making price comparisons internationally; however, these public prices do not reflect the confidential price adjustments negotiated with some insurers that have become systemic in Canada and around the world. In an era marked by high-cost specialty medicines, the level of confidential price adjustments negotiated can be substantial. This means that there is a growing discrepancy between public list prices and lower actual prices paid in the market and leaves the PMPRB to regulate on the basis of public prices that bear less and less resemblance to what insurers are actually paying in the market. The PMPRB needs other factors that it can use to assess whether a price is excessive.

The schedule of comparator countries

The schedule to the Regulations sets out the seven countries for which patentees are to submit price information. The PMPRB uses the prices of the same patented medicines in these countries, where available, to set price limits on medicine prices in Canada at introduction and in subsequent years. The schedule of countries to the Regulations has not been updated since the Regulations were first conceived 30 years ago. At that time, policy makers believed that patent protection and price were key drivers of medicine R&D investment. The choice was made to offer a comparable level of patent protection and pricing for medicines as existed in countries with a strong medicine industry presence, on the assumption that Canada would come to enjoy comparable levels of R&D. However, the percentage of R&D-to-sales by patentees in Canada has been falling since the late 1990s and is currently less than Canada obtained at the time of the 1987 *Patent Act* reforms. By comparison, and despite Canada having among the highest patented medicine prices, industry R&D investment relative to sales in the PMPRB7 countries is on average 22.8% versus 4.4% in Canada. As a result, there is no evidence of a determinant link between domestic prices and the location of industry R&D investment. Other factors, such as head office location, clinical trials infrastructure and scientific clusters, appear to be much more influential determinants of where medicine investment takes place in a global economy.

The policy intent of the original schedule selection has not materialized and is no longer considered to be the most appropriate basis for the composition of the countries listed in the schedule. The regulatory requirements for patentees to report on prices in the PMPRB7 keep Canadian prices for patented medicines among the highest in the world.

Issues

The Board determines whether a price is excessive based on the price regulatory factors in the Act, and the patentee price information reporting requirements specified in the Regulations. The evolution in the global and Canadian medicine environment has made apparent two important limitations to the Board's current regulatory framework: (1) the ineffectiveness of the current price regulatory factors to adequately inform the PMPRB's assessment of excessiveness; and (2) the insufficiency of the patentee price information reporting requirements.

Under the current regulatory framework, excessiveness is assessed almost entirely on the basis of domestic and international public list prices. This is problematic with an influx in high-cost specialty medicines and list prices not reflective of what public and private insurers are actually paying. The main limitations of the current framework are that

- It does not provide additional price regulatory factors, beyond price comparisons and CPI, for the PMPRB to assess whether a price is excessive. It does not consider whether the price of a medicine reflects
- **The value of a medicine to a patient:** medicines that offer substantial clinical benefits to patients or are alone in their therapeutic class will be in greater demand than medicines that are only marginally better than the standard of care or are one among many in their class;
- **The number of patients that can benefit from a medicine:** the size of the market for a medicine can have an impact on its expected price and the ability to pay for the medicine in a given country; and
- **The wealth of a country:** countries with greater economic resources can afford more or higher-cost medicines than countries with fewer resources.
- The list of countries used for price comparisons (PMPRB7) is out of date. Canadian prices for new medicines are compared to those of countries with high medicine prices, rather than to those of countries with similar medicine markets, consumer protection and wealth. The selection of countries can have a significant impact on the price maximums for patented medicines in Canada. As the PMPRB relies on international price comparisons, the PMPRB7 set of comparator countries has the effect of allowing higher prices in Canada than would otherwise be the case if comparator countries were more reflective of the Canadian medicine market.

Objectives

The proposed amendments to the *Patented Medicines Regulations* would ensure that the PMPRB is equipped with the price regulatory factors and patentee price information reporting requirements necessary to fulfill its mandate to protect Canadian consumers from excessive prices for patented medicines. It is anticipated that the implementation of these amendments by the PMPRB would lead to lower prices for patented medicines in Canada that are more closely aligned with their value to patients and the health care system, and Canadians' willingness and ability to pay.

Description

There are five elements included in the proposed amendments.

Price regulatory factors and updating the schedule of comparator countries

1. Introduce new, economics-based price regulatory factors that would enable the PMPRB to ensure non-excessive prices that reflect value and Canada's willingness and ability to pay for patented medicines.
2. Update the schedule of countries used by the PMPRB for international price comparisons to be better aligned with the consumer protection mandate of the PMPRB and median OECD prices.

Reporting requirements

3. Reduce reporting obligations for patented veterinary, over-the-counter and "generic" medicines.
4. Set out the information reporting requirements to enable the PMPRB to operationalize the new price regulatory factors.

5. Require patentees to report price and revenue information that is net of all domestic price adjustments such as direct or indirect third party discounts or rebates and any free goods or services.

A more detailed description of each of the proposed amendments follows.

1. Introduce new, economics-based price regulatory factors that would ensure prices reflect value and Canada's willingness and ability to pay for patented medicines

This proposed amendment would introduce three additional price regulatory factors of pharmacoeconomic value, market size, and gross domestic product (GDP) and GDP per capita in Canada. These new price regulatory factors would enable the PMPRB to consider complementary and highly relevant aspects of price excessiveness related to the value of the health benefit produced by the medicine, and the willingness and ability of Canadian consumers to pay for it. These new factors will only apply to sales of patented medicines that occur after the coming into force of the proposed amendments.

Pharmacoeconomic value of the medicine in Canada

The price paid for a medicine should take into consideration the value it produces. At the same time, it must recognize the cost to supply the medicine if manufacturers of medicines are to continue to invest in the production of new medicines. A pharmacoeconomic evaluation identifies, measures, and compares the costs and benefits of a given medicine to patients and the health care system. The inclusion of this factor would require the Board to consider whether a medicine's price is commensurate with the benefits it provides to patients within the context of the Canadian health care system.

Size of the market for the sale of the medicine in Canada and in countries other than Canada

The addition of this factor in the Regulations could enable the PMPRB to develop market impact tests for medicines that are likely to pose affordability challenges for insurers due to the market size for the medicine. The impact of an excessive price is a function of both price and volume; the larger the size of the market for the medicine in Canada, the greater the impact of its price. Where public and private insurers are called on to cover the cost of a medicine for a significant number of patients, the high cost of a medicine could render the medicine unaffordable for all who need it. The Canadian price could be assessed against international prices and prevalence (number of people with the disease) levels in an effort to evaluate the price-volume relationship and establish a reasonable market impact test. Including the size of the market as a factor would also allow the PMPRB to reassess the prices of patented medicines over time. Once a medicine is on the market, the patentee may seek regulatory approval from Health Canada to use the medicine in the treatment of other conditions, or the medicine might also be prescribed by physicians off-label (i.e. prescribed for the treatment of conditions for which the medicine has not received regulatory approval). Since patented medicines are protected from new entrants, their prices can remain unaffected from subsequent fluctuations in the size of the market into which they may be sold. As patentees are assumed to set their introductory prices at a profitable level to recoup initial investment, a growth in the market size should align and correct prices downwards to a comparable level. Failure to do so could suggest that the original price, for an expanded market, is now excessive.

GDP in Canada and GDP per capita in Canada

The GDP is a measure of a country's economic output. GDP growth measures how much the inflation-adjusted market value of the goods and services produced by an economy is increasing over time. Per capita GDP measures how much a country is producing relative to its population. Growth in Canadian GDP can be taken as an indicator of the country's ability to pay year-over-year, whereas per capita GDP is a proxy for buying power at the level of the individual. The introduction of GDP in Canada and GDP per capita in Canada as a price regulatory factor would provide the PMPRB with measures of ability to pay for medicines at the national and individual level. The inclusion of this factor would allow the PMPRB to assess the impact of a medicine's price on the finances of consumers and insurers. It could also enable the PMPRB to develop market impact tests for medicines that are likely to pose affordability challenges for insurers due to the market size for the medicine.

2. Update the schedule of countries used by the PMPRB for international price comparisons to be better aligned with the PMPRB's consumer protection mandate and median OECD prices

The PMPRB uses the publicly available list prices of patented medicines sold in the PMPRB7 to set maximum prices for the same patented medicines in Canada at introduction and in subsequent years. Depending on their price levels, the selection of countries can have a significant impact on the maximum prices for patented medicines in Canada.

This proposed amendment would reconsider the PMPRB7 to update the list of countries set out in the schedule to be better aligned with the PMPRB's consumer protection mandate, and Canada's wealth and status as a major market for medicines. The scope of countries considered for the revised schedule was the 35 OECD countries, as they share the same economic and social policies as Canada. Requiring patentees to report on prices in all 35 member countries was deemed unnecessary because (1) this would present a significant reporting burden; (2) some OECD countries are better aligned with Canada's domestic policy priorities and economic standing; and (3) it may be difficult to obtain price and sales information from some countries. Three criteria were used to select a subset of OECD countries to form the revised schedule.

First, the countries must have medicine pricing policies that are well aligned with the consumer protection mandate of the PMPRB, such as a country having national pricing containment measures to protect consumers from high medicine prices. For example, the United States does not satisfy this criterion.

Second, countries must possess reasonably comparable economic wealth as Canada, such as a country having a similar economic standing to Canada, as measured by GDP per capita. This is to ensure that prices correspond to Canada's ability to pay for medicines. For example, Canada's GDP per capita ranks eleventh among OECD countries, but prices for patented medicines are the third highest. The proposed schedule includes countries that have reasonably higher, similar and lower GDP per capita as Canada.

Third, countries are required to have a similar medicine market size characteristics as Canada, such as population, consumption, revenues and market entry of new products. This is to ensure that the resulting similar-sized markets produce a price level that is commensurate with Canada's share of global medicine sales.

Using these criteria, the proposed schedule lists Australia, Belgium, France, Germany, Italy, Japan, the Netherlands, Norway, South Korea, Spain, Sweden and the United Kingdom (PMPRB12). Including a larger number of countries in the schedule would make price tests less sensitive to the influence of countries with

prices that are high or low, and reduce the impact where price and sales information is delayed or not available. For example, with only seven reference countries, delayed or missing price information from just two of the reference countries could impact the sample median by as much as 10%. Increasing the schedule to 12 countries would reduce this impact to just 2%. This slightly larger list would provide the PMPRB with a more balanced perspective of prevailing market prices and greater stability of the sample median without imposing significantly greater reporting requirements on patentees or administrative burden on the PMPRB.

3. Reduce reporting obligations for patented veterinary, over-the-counter and “generic” medicines

The Regulations currently only require patented veterinary and over-the-counter medicines (that do not contain a controlled substance or are not a radiopharmaceutical or biologic as per the *Food and Drugs Act* and the *Food and Drug Regulations*) to report price and sales information to the PMPRB on a complaints basis. Proposed amendments would further reduce reporting obligations for these medicines so that price, sales, and identity information would only be required on request by the PMPRB for all patented veterinary and over-the-counter medicines, including those that may contain a controlled substance, or are a radiopharmaceutical and/or a biologic. Amendments would also extend the same reduced reporting obligations to patented generic medicines (i.e. medicines approved by means of an ANDS). Patentees of generic medicines typically face greater competition, and the risk of excessive pricing due to market power is generally not cause for concern. These proposed amendments are intended to spare patentees unnecessary reporting regulatory burden for medicines that pose a lower risk of excessive pricing. It would also allow the PMPRB to focus its resources on medicines that pose a more substantive risk of excessive pricing.

4. Set out the patentee pricing information reporting requirements to enable the PMPRB to operationalize the new pricing factors

The current Regulations specify what information patentees must provide to the PMPRB in support of the current price regulatory factors. This includes information about the prices of patented medicines sold in Canada and other countries, patentees’ revenues and R&D expenditures. Patentees would be required to report new information to the PMPRB to support the new pharmacoeconomic value and market size factors. Patentees would not be required to report on information related to GDP and GDP per capita, as this information would be obtained from Statistics Canada.

Information regarding pharmacoeconomic value: patentees would be required to provide the PMPRB with all published cost-utility analyses that express the value in terms of the cost per quality-adjusted life year (QALY). Cost-utility analyses are viewed by experts as the “gold standard” approach to considering the economic value of new medicines. The cost per QALY quantifies benefit by measuring lengthened life and/or improved quality of life. It is the most established measure of pharmacoeconomic value, as it enables comparisons across different types of medicines by using a common unit of measurement. This information reporting requirement would enable the PMPRB to consider the introduction of the concept of a maximum cost per QALY threshold in Canada.

In recognition of the significant expertise that can be necessary to prepare and validate cost-utility analyses, reporting would be limited to those that have been prepared by a publicly funded Canadian organization, such as the Canadian Agency for Drugs and Technologies in Health (CADTH) or the Institut

national d'excellence en santé et services sociaux (INESSS). These organizations have dedicated expertise, and they generally conduct pharmacoeconomic analyses for medicines seeking to be reimbursed by public insurers. The PMPRB would consider these analyses in its evaluation of price excessiveness. It would not duplicate the work conducted by CADTH and INESSS as part of reimbursement processes.

Even though the new pharmacoeconomic value factor would only apply to sales of patented medicines made after the coming into force of the amended Regulations, the obligation to submit the most recently published cost-utility analysis would extend to all patented medicines, both those marketed as of the date of the amended Regulations coming into force and any new medicines offered for sale following the date of the coming into force. Cost-utility analyses are typically only prepared for a given medicine following certain trigger points in a medicine's life cycle (e.g. at time of initial market launch or following regulatory approval for use of the medicine in the treatment of a new condition). Although the most recent cost-utility analysis for an existing medicine could be several years old, it would still reflect the most recent and relevant information for the PMPRB to consider when applying the new factor of pharmacoeconomic value. Patentees would only be required to provide published analyses — there would be no obligation on the patentee to prepare a cost-utility analysis if one does not exist.

Information respecting market size: patentees would be required to provide the PMPRB with information on the estimated maximum use of the medicine in Canada, by quantity of the medicine sold in final dosage form, for each dosage form and strength that are expected to be sold. It is expected that patentees already construct this estimate as part of their development plans to introduce a new patented medicine to the Canadian market. Patentees compile this information in the development of business plans and for CADTH processes. Before going to market, patentees rely upon available statistics and information on the prevalence (number of people with a disease) in a given country and incidence (estimated number of new cases each year) to develop a sales forecast. They also take into account other factors such as competition to estimate the potential market share for their new medicine.

Patentees would also be required to provide the PMPRB with updated estimates that may occur, for example, when a medicine receives approval from Health Canada for use in the treatment of a new condition that expands the estimated market for the medicine. The new factor of market size would only apply to sales of patented medicines made after the coming into force of the amended Regulations. However, in view of the fact that it can take up to three years for the market for a new medicine to fully mature, patentees of medicines that are already on the market and were first offered for sale within three years prior to the amended Regulations coming into force or have received regulatory approval for use in the treatment of a new condition within this same three-year period would be required to provide information on the estimated maximum use of these medicines in Canada.

5. Require patentees to report price and revenues, net of all price adjustments

The Regulations currently require patentees to report information on price adjustments for the first point of sale only. Patentees are not required to report the significant price adjustments they may provide to third party insurers such as provincial insurers that provide reimbursement for the cost of a medicine sold to a patient. Provincial insurers are some of the biggest payers of patented medicines in Canada. Without this information, the PMPRB sets the non-excessive price maximum of a medicine on the basis of information that only includes some price adjustments. This amendment would require patentees to report price and revenue information that is net of any price or other adjustments, including discounts, rebates and free goods and services, to any party that pays for, or reimburses, the medicine. Although most adjustments are

likely to result in a price reduction, this amendment is intended to capture information on any adjustment including those resulting in a price increase. This information would be considered privileged as per section 87 of the *Patent Act* and would be considered by the Board when determining excessiveness.

With this information, the PMPRB would use the price that is net of any price adjustments to calculate the non-excessive price maximum. The PMPRB currently regulates the non-excessive price of a medicine based on the prices of other medicines in the same therapeutic class for sale in Canada. Since that price information does not include third-party price adjustments, the prices of comparator products that subsequently enter the market are often inflated (as the price ceilings for those medicines are determined in relation to an inflated list price of the existing medicine, rather than the actual price paid in Canada). As a result, the therapeutic class comparison tests yield price maximums that are higher than they would be if the actual price paid were available to the PMPRB. Compelling actual price information, inclusive of all price adjustments provided by the patentee, would allow the PMPRB to include rebates in the calculation of the average transaction price. It would also provide a mechanism for patentees to comply with the regime by calculating a true transaction price reflective of all rebates and discounts, direct and indirect.

Regulatory and non-regulatory options considered

Status quo

The option of taking no action was considered and rejected on the grounds that the PMPRB's current regulatory framework lacks effective price regulatory factors and sufficient patentee price information reporting requirements. The current factors do not take into account all the aspects of excessiveness for new categories of medicines that have emerged since the creation of the PMPRB. The PMPRB's current patentee price information reporting requirements produce incomplete domestic pricing information and provide international price information from a number of countries with high patented medicine prices that are not equivalent to the Canadian market.

Non-regulatory modernization (updates to the PMPRB's *Compendium of Policies, Guidelines and Procedures*)

This option would be primarily limited to revised price tests that continue to rely completely on domestic and international price referencing methods. This option was fully explored, and included a stakeholder consultation by the PMPRB in 2016, but was rejected on the grounds that simply updating the guidelines does not address the underlying inadequacies of the existing Regulations. Regulatory reform is needed to obtain all price adjustment information and lessen the current dependence on international price testing through the addition of new factors. Under a modernized regulatory framework, the PMPRB would have a stronger basis from which to modernize its guidelines.

Benefits and costs

The quantitative benefits from the cost-benefit statement relate to lower overall spending on patented medicines in Canada that is anticipated to result from lower prices. The quantified costs relate to (1) reduced industry revenues due to lower prices for patented medicines; (2) the net impact of new and reduced administrative industry reporting requirements; and (3) the costs to the Canadian government to ensure compliance with the proposed amendments.

The total quantified benefit of lower patented medicine prices is estimated at \$21.3 billion (PV) over 10 years. The total quantified cost of this proposal, including all of the industry's lost revenues, is estimated at \$8.6 billion (PV) over 10 years. Administrative costs to industry and the Government of Canada are anticipated to be approximately \$62 million (PV) over 10 years. The total net benefits of the proposed amendments are estimated to be \$12.7 billion (NPV) over 10 years, from 2019 to 2028. A discount rate of 7% was used in all PV calculations. The complete cost-benefit analysis is available upon request.

Cost-benefit statement

Quantified impacts (CAN\$, 2017 price level/constant dollars)				
	Base Year (Year 1)	Final Year (Year 10)	Total (PV)	Annualized Average
Benefits				
Lower drug expenditure	\$219,993,857	\$2,782,694,694	\$8,567,004,599	\$1,219,745,515
• New factors	\$33,443,984	\$1,399,184,431	\$3,763,190,611	\$535,792,273
• Updated schedule	\$138,187,981	\$770,272,294	\$2,788,004,256	\$396,948,040
• Third-party price adjustments	\$48,361,892	\$613,237,969	\$2,015,809,732	\$287,005,201
Health care system	\$425,688,113	\$5,384,514,233	\$12,722,001,829	\$1,811,322,089
Total benefits	\$645,681,970	\$8,167,208,927	\$21,289,006,428	\$3,031,067,604
Costs				
Industry			\$8,567,068,356	\$1,219,754,583
• Loss revenues	\$219,993,857	\$2,782,694,694	\$8,567,004,599	\$1,219,745,515
• Administrative cost (includes regulatory burden reduction)			\$34,717	\$4,924
• Compliance cost			\$29,106	\$4,144
Government	\$4,981,481	\$8,025,361	\$61,716,822	\$8,787,064
• PMPRB program expenditure	\$3,849,215	\$5,680,633	\$43,361,629	\$6,173,704
• Special purpose allotment	\$981,481	\$2,025,361	\$16,119,394	\$2,295,033
• Accommodation requirements	\$143,085	\$304,667	\$2,131,142	\$303,425
• IT services	\$7,700	\$14,700	\$104,657	\$14,900
Total costs (PV)			\$8,628,785,178	\$1,228,541,647

Net benefits (NPV)	\$12,660,221,250	\$1,802,525,957
Qualitative impacts		
<ul style="list-style-type: none"> • Greater population health and increased savings to the health care system due to fewer acute care incidents. Lower prices could result in lower patient cost-related non-adherence to needed medicines (for example not filling prescriptions or skipping doses). • Providing the opportunity to improve access to drugs and reallocate resources to other important areas of the health care system. • Reduction in the burden placed on price negotiating bodies (e.g. the pan-Canadian Pharmaceutical Alliance) to ensure system affordability. • Potential impact on wholesalers, distributors, pharmacies, and generic medicine manufacturers whose markups and prices are often expressed as a percentage of patented medicines prices. 		

Costs

Patentee price information reporting requirements already exist under the current regulatory framework. For the most part, the types of information to be reported and the reporting frequency would remain unchanged. The increased administrative burden on the industry would be to report in relation to the new price regulatory factors. The proposal also includes the benefit of reduced administrative burden for certain types of medicines (patented over-the-counter, veterinary, and ANDS-approved medicines), but this reduction would not be sufficient to fully offset the new reporting requirements.

Industry

Industry costs would include the

- Reporting requirements on the new price regulatory factors. Patentees would ensure that the information be updated as new analyses are undertaken. Total administrative costs to report in relation to the new price regulatory factors are estimated to be \$6,175 annually or \$43,373 in PV over 10 years.
- Compliance cost to update reporting systems to include the proposed schedule of countries on which patentees must report pricing information every six months, and updating their domestic prices and net revenues to include all price adjustments. Patentees already have reporting systems in place for domestic and international prices — the proposal only modifies the type of information to be reported. Total compliance costs are estimated to be \$4,144 annually or \$29,106 in PV over 10 years.

Administrative burden reduction

The proposal removes the need for patented veterinary, over-the-counter, and generic drugs to file identity and price information with the PMPRB, unless that information is requested by the PMPRB. There are 96 medicine products (out of PMPRB's 1 359) that fall into these categories and are currently required to file information with the PMPRB. Given that the Federal Court of Appeal only recently clarified and upheld the PMPRB's jurisdiction over these medicines, the compliance for reporting of these medicines has not historically been considered by the PMPRB. Assuming full compliance, the administrative burden reduction is expected to be \$8,656 (PV) over 10 years.

Lost revenues to the medicine industry

The PMPRB only regulates excessive patented medicine prices in Canada. Any price reduction and repayment of excess revenues that would occur as a result of this proposal would be pursuant to a voluntary compliance undertaking (VCU) by the patentee to comply with the new maximum compliant price levels, or pursuant to a Board Order made following a public hearing before the Board where a Board Panel determines that the medicine has been sold at an excessive price. It is estimated that this proposal will result in reduced industry revenues of approximately \$8.6 billion (PV) over 10 years, due to reduced thresholds for maximum non-excessive prices in Canada. For the purpose of this cost-benefit analysis (CBA), national treatment of revenue was given to all patented medicine manufacturers in Canada, despite the fact that 90% of the companies that report to the PMPRB are multinational enterprises (MNEs).

Government of Canada

Increasing the PMPRB's capacity

Costs to Government would include funds for the PMPRB to hire additional staff to support the expected increase in enforcement-related activities, and to administer the new price regulatory factors. The base (2018–19), second (2019–20), third (2020–21), and fourth years (2021–22) would be anticipated to cost \$3.8 million, \$5.7 million, \$6.7 million, and \$7.7 million, respectively. From the fifth year onwards, it is anticipated that costs to Government would be \$5.7 million/year to maintain the PMPRB's increased capacity.

Increasing special purpose allotment funding

With the proposed new Regulations in place, patentees might be less willing to offer voluntary compliance undertakings and instead press for formal and potentially prolonged hearings. The PMPRB would require additional funding for its special purpose allotment (SPA) to cover the costs of outside legal counsel and expert witnesses. Patentees might also more frequently challenge decisions made under the new regime in the Federal Court. The base (2018–19), second (2019–20), third (2020–21), and fourth years (2021–22) would be anticipated to cost \$1.0 million, \$1.8 million, \$2.8 million, and \$3.8 million, respectively. From the fifth year onwards, it is anticipated that costs to Government would be \$2.0 million/year to maintain the PMPRB's increased SPA funding.

Offsetting costs to Public Service and Procurement Canada and Shared Services Canada

Increasing the PMPRB's staffing levels would also increase accommodation and information technology (IT) costs. Combined, the base (2018–19), second (2019–20), third (2020–21), and fourth years (2021–22) would be anticipated to cost \$151,000, \$305,000, \$328,000, and \$331,000, respectively. From the fifth year onwards, it would be anticipated that costs to Government would be \$319,000/year to offset Public Service and Procurement Canada's accommodation costs and Shared Services Canada's IT services costs.

The total cost to the Government of Canada would be anticipated at \$61.7 million in net present value over 10 years.

Benefits

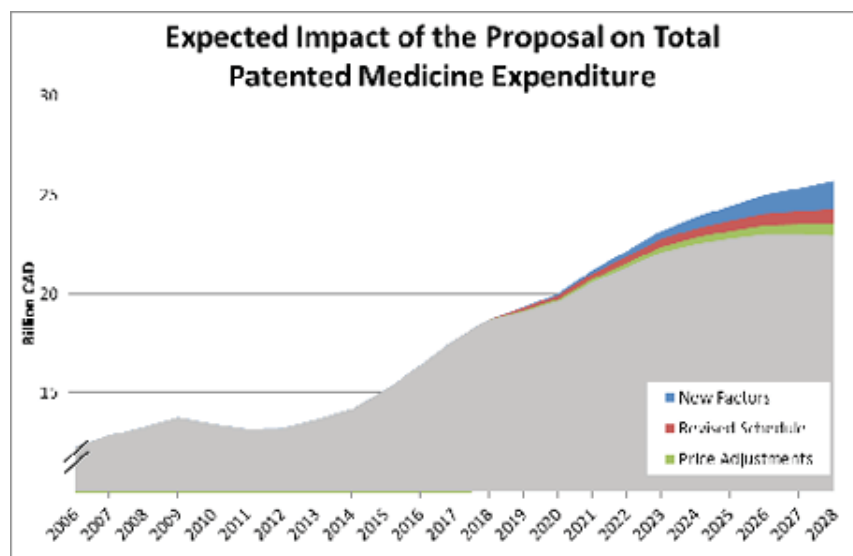
Benefits were calculated based on the expected reduction in the level of public risk of excessively priced patented medicines in Canada.

Anticipated quantitative benefits were calculated on the basis of reduced overall spending on patented medicines. The projected baseline of future spending (2017–2028) was calculated using current growth trends and anticipated launches from the current medicine pipeline. It also includes the expected loss of patent protection of medicines that are currently under the PMPRB's jurisdiction. The total net benefits arising from the proposed amendments are estimated to be \$25.1 billion dollars (NPV) over 10 years.

Lower patented medicine expenditure

The proposed amendments are expected to lower patented medicine expenditure by an estimated \$8.6 billion (PV) over 10 years.

The introduction of the new price regulatory factors would be expected to have the biggest impact on patented medicine expenditure (\$3.8 billion), followed by the revised schedule (\$2.8 billion) and the reporting of price and sales adjustment with third parties (\$2.0 billion).



Healthcare system benefits

Without the proposed amendments, it is estimated that public health care systems from across Canada will spend an additional \$3.9 billion (PV) for the same quantity of patented medicine. This represents a significant opportunity cost for the Canadian public health care system, as these funds could have been used in other areas of the health care system to better the health of Canadians. Given the large ripple effects on health and the economy for every dollar spent in public health, ([see footnote 1](#)) the size of this opportunity cost in Canada is quite substantial. The total opportunity cost to the health care system of paying for excessively priced medicines was estimated to be \$12.7 billion dollars (PV) over 10 years.

Sensitivity analysis summary

A sensitivity analysis was performed in relation to two variables that could greatly affect the estimated impact of the proposal. The first variable relates to the PMPRB implementation of the proposal and the other to the projected growth rate in patented medicine expenditure. The baseline analysis was conducted on an assumption that the PMPRB continues to apply price test methods that are similar to those currently in place. This assumption is necessary since any changes to the guidelines are fully within the control of the PMPRB. For example, the PMPRB currently uses the median PMPRB7 price to test new medicines against prices in other countries. The baseline assumes that the median price test would also be applied to the new

PMPRB12. The sensitivity analysis of this variable examined possible alternate approaches to the existing price regulatory factors as well as possible approaches to implementation of the proposed new factors in the guidelines.

The second variable relates to the growth of expenditures in patented medicines. If growth in patented medicine expenditure is higher than anticipated, the benefit measured in dollars, calculated from a percent reduction due to lower patented medicine prices, will be higher than anticipated. Likewise, if growth in expenditure is lower than anticipated, then the overall benefit will also be lower. Growth in the patented medicine industry is difficult to predict, and the emergence of new types of patented medicines, such as biologics, introduces new uncertainties into modelling efforts.

The sensitivity analysis demonstrates that total patented medicine expenditure could be lowered from a minimum of \$6.4 billion dollars (PV) after 10 years to a maximum of \$24.9 billion dollars (PV) after 10 years. The minimum sensitivity analysis impact represents the lowest projected patented medicine sales growth coupled with the least aggressive reforms to the PMPRB guidelines. The maximum sensitivity analysis impact represents the highest projected patented medicine sales coupled with the most aggressive reforms to the PMPRB guidelines. The current CBA estimates the baseline cumulative expenditure after 10 years to be \$8.6 billion dollars (PV). (see footnote 2)

Distributional analysis summary

The vast majority of patented medicine manufacturers are located in Ontario, Quebec, British Columbia, and Alberta. These four provinces constitute 98% of all companies that would be affected by the proposed amendments.

All — public, private, and out-of-pocket — payers of patented medicines from across the country will benefit from lower prices.

Usage by age and gender: According to Statistics Canada's report "Prescription medication use by Canadians aged 6 to 79," prescription medicine use rose with age from 12% among 6- to 14-year-olds to 83% among 65- to 79-year-olds. Prescription medicine use was also associated with the presence of physical and mental health conditions. The percentage of Canadians taking prescription medicines did not differ by household income. Females were generally more likely than males to report taking prescription medications (47% versus 34%). However, at ages 6 to 14, a higher percentage of boys, rather than girls, used prescription medications, and at ages 65 to 79, the prevalence of prescription drug use was similar for men and women. Prescription drug use intensity — the number of different medications taken — was strongly associated with age. The percentage taking more than one medication rose from 3% at ages 6 to 14 to 70% at ages 65 to 79.

“One-for-One” Rule

The estimated added regulatory burden to patentees was calculated to be approximately \$43,373, with an estimated reduction in regulatory burden of \$8,656, for a total of \$34,717 (PV over 10 years). This calculation includes the upfront cost of providing the PMPRB with cost-utility and market size analyses for medicines currently under the jurisdiction of the PMPRB, the ongoing costs of updating these analyses and providing the PMPRB cost-utility analyses and market size estimates for all new patented medicines that enter the market, as well as further reducing the current reporting requirements for patented veterinary, over-the-counter medicines, and adding generic medicines to those same reduced reporting obligations. The proposal is considered an “IN” under the “One-for-One” Rule and has an estimated impact of \$3,062.

Current initiative is an:	"1N" ("One-for-One" Rule)		
	Values to Report in Regulatory Impact Analysis Statement	Rounding	Unit of Measure
Annualized administrative costs (constant \$2012)	\$3,062	0 digits	Constant 2012 dollars, present value base year: 2012
Annualized administrative costs per business (\$2012)	\$40	0 digits	Constant 2012 dollars, present value base year: 2012

Small business lens

The small business lens does not apply to the proposed amendments, as only medicine manufacturers that have a patented medicine for sale in Canada would be affected by the proposed amendments. Among the 77 companies reporting to the PMPRB, none were identified as satisfying the small business definition. In general, patented medicines are sold by multinational enterprises or their subsidiaries.

Consultation

The consultation period for prepublication in the *Canada Gazette*, Part I, of the regulatory proposal will be 75 days.

This consultation builds on an initial consultation on the regulatory proposal. On May 16, 2017, the Honourable Jane Philpott, former federal Minister of Health, announced the launch of the consultation on the proposed amendments to the *Patented Medicines Regulations*. A consultation document entitled "Protecting Canadians from Excessive Drug Prices: Consulting on Proposed Amendments to the Patented Medicines Regulations" was posted on Health Canada's website as well as the Government of Canada's Consulting with Canadians website. The consultation was promoted through a news release and an email notification that was distributed widely to stakeholders. In addition, to comply with subsection 101(2) of the *Patent Act*, Minister Philpott wrote each of her counterparts in the provinces and territories, inviting comments on the proposed regulatory amendments. Written submissions from all stakeholders and interested parties were accepted until June 28, 2017. During the consultation period, Health Canada hosted nine engagement sessions with external stakeholders, including representatives from public and private insurers, patient organizations, the medicine industry, the health professions and academia.

Insurers (public and private) were supportive overall, noting that pharmacoeconomic value and market size are very relevant to the determination of price excessiveness. There was no consensus around GDP as a factor. Private insurers suggested that the factors account for considerations relevant to employers, such as the impact of the medicine on productivity, absenteeism, and disability claims. Insurers supported the revised schedule of countries. While in favour of reducing regulatory burden for patented generic medicines, insurers suggested that the PMPRB still request price and sales information for patented generics at risk of higher prices. Finally, insurers were supportive of the amendment to provide the PMPRB with price adjustment information, on the condition that this information remain confidential to the PMPRB.

Patient organizations noted that the high prices of new patented medicines pose a financial barrier to access for Canadians and asked that the Regulations ensure that patient access to medicines is a primary concern. Patient organizations suggested that there be enough flexibility in the Regulations to allow the PMPRB to go beyond the cost per QALY to take patient preferences into account and to consider special circumstances such as medicines for rare diseases. In addition, organizations asked that the use of price adjustment information in regulating prices not compromise the bargaining position of insurers.

Representatives of the brand name medicine industry suggested that proposed amendments would add significant complexity and uncertainty for patented medicines to reach the market in Canada. A number of representatives suggested that the proposed economic-based factors go beyond the mandate of the PMPRB and are potentially duplicative of CADTH's assessment. They expressed concern around the additional regulatory burden of providing international pharmacoeconomic and pricing information. A common suggestion was that the United States should remain in the schedule of countries. It was recommended that the Regulations allow for a risk-based approach and that regular reporting requirements should be removed for lower-risk products. It was not clear to the industry how the PMPRB plans to use and protect confidential price adjustment information; however, it was suggested that providing this information to the PMPRB would risk lower price adjustments for insurers in Canada.

Generic medicine industry representatives supported the proposal to remove the requirement for patented generic manufacturers to regularly report information about the identity and price of these medicines, as they pose a low risk of abusing market power and are subject to price regulation by the provinces and territories. They recommended this amendment be extended to include other complex forms of generics that do not receive a Declaration of Equivalence from Health Canada, such as biosimilars and generics with complex ingredients and formulations.

The consumer health products industry acknowledged that the over-the-counter products (OTCs) it produces are already exempt from reporting regularly. Representatives recommended that all self-care products be exempt entirely from the patented medicine framework; however, it is beyond the scope of the Regulations to change the PMPRB's jurisdiction over patented medicines.

Representatives from physicians' and nurses' associations supported economics-based factors to assess the value of a medicine, the revised schedule and requiring information on confidential rebates in Canada. Nurses' associations were not supportive of exempting patented generics from systematic reporting requirements. Pharmacists supported assessing a medicine based on its value, but noted that pharmacoeconomic value should consider benefits and costs beyond a QALY. They noted that the schedule of comparator countries should be revised based on the availability of products in each country and asked that the amendment pertaining to confidential price adjustments not compromise the price adjustments negotiated by public insurers.

Academics supported the proposed pharmacoeconomic value factor and cost per QALY information requirement. Some academics supported using GDP to set an upper bound on prices and suggested the use of per capita GDP. Academics were less convinced that market size information would be useful without more information on the R&D costs of a medicine. Most agreed with revising the schedule and removing countries that do not have consumer protections in place for excessive prices. Academics were generally in favour of allowing the PMPRB to collect information on adjustments in price, but they suggested it be broadened to include all types of transfers from patentees that impact prices, including pay-for-performance agreements, and cautioned against using rebate information when making international comparisons.

The responses related to the Regulations have been taken into consideration in the development of this proposal for prepublication in the *Canada Gazette*, Part I, and the Regulatory Impact Analysis Statement. In particular,

- The economics-based price regulatory factors in the proposed amendments have remained broad in order to provide the PMPRB with the flexibility to consider other measures beyond the cost per QALY where relevant, and to enable the PMPRB to develop appropriate measures using market size and GDP. Based on feedback received, GDP per capita has been added to the GDP factor.
- The information reporting requirements for patentees have been revised to minimize the regulatory burden while providing the PMPRB with sufficient information to protect Canadians from excessive prices. The proposed amendments do not require cost-utility analyses (CUAs) from countries other than Canada to be reported.
- Further analysis has been provided on the proposed schedule; an estimate of the impacts on patented medicine expenditures is provided in the cost-benefit analysis.
- Consideration was given to the removal of systematic information reporting requirements for patentees for other low-risk products beyond patented generic medicines. It is proposed that regular reporting requirements be removed for all patented over-the-counter medicines, including radiopharmaceuticals and biologics authorized for sale under the *Food and Drug Regulations* as well as those containing controlled substances. While other products such as biosimilars and other patented generic medicines that are not authorized for sale by way of an ANDS were considered, these products and their risk of excessive pricing could not be adequately defined.
- It is proposed that the new information reporting requirements in the Regulations capture all price adjustments that would serve to lower (e.g. discounts, rebates, free goods, free services) or raise (e.g. payment for performance) the price of a medicine.

Regulatory cooperation

This proposal would update the schedule of countries used by the PMPRB for international price comparisons to be better aligned with the PMPRB's consumer protection mandate and median OECD prices. This international alignment would contribute to lowering medicine prices for Canadians.

Rationale

Unlike most international health systems, Canada's health system does not have a single payer for medicines. Canadian expenditure on prescription medicines is split between public insurers (43%), private insurers (35%) and Canadians paying out-of-pocket (22%).

Modernization of the PMPRB's regulatory framework would benefit all those who pay for medicines in Canada through a higher standard of consumer protection. Canada's public and private insurers would benefit from lower maximum prices so their price negotiations achieve more than simply prices that match those in other countries. The amendments would help the PMPRB to achieve Canadian maximum prices closer to international norms. This would allow public and private insurers to negotiate with sellers on a more equal footing with health authorities in other countries. Employer-sponsored health insurance plans are anticipated to benefit from lower premiums and reduced risk of becoming untenable due to high-cost medicines. Uninsured Canadians who pay out-of-pocket for their medicines rely most heavily on the consumer protection mandate of the PMPRB, and they would benefit from lower prices for their patented medicines.

This proposal is anticipated to result in an estimated total benefit to Canadians of \$8.6 billion in net present value (NPV) over 10 years following implementation.

Implementation, enforcement and service standards

The proposed Regulations would come into force on January 1, 2019. This would allow patentees time to prepare for implementation of the new price regulatory factors and information reporting requirements on prices. January 1, 2019, was the date chosen to align the implementation with the PMPRB's reporting periods of January 1 and July 1. Once the amended Regulations are published in the *Canada Gazette*, Part II, responsibility for implementation, enforcement and service standards would be passed to the PMPRB. This is anticipated to include the finalization of a PMPRB-led stakeholder consultation on a revised *Compendium of Policies, Guidelines and Procedures* that will be used to reach an understanding of how the revised framework would be embodied in the form of specific price tests and qualifying information to be reported by patentees.

The new factors may only be considered in relation to sales that occur after the coming into force of the proposed amendments. However, the reporting requirements in the amended Regulations would be applied to new and existing patented medicines alike. Patentees of existing medicines would have 30 days after the coming into force to provide the cost-utility analysis (if available) and estimated market use information (if applicable). Price information for the countries in the revised schedule and domestic price and revenue information that takes into account price adjustments would first be required to be reported within 30 days after the end of the reporting period in which the proposed amendments came into force (i.e. within 30 days after June 30, 2019).

Contact

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Executive Director
Office of Pharmaceuticals Management Strategies
Strategic Policy Branch
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70 Colombine Driveway, Tunney's Pasture
Ottawa, Ontario
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PROPOSED REGULATORY TEXT

Notice is given that the Governor in Council, pursuant to subsection 101(1) ([see footnote a](#)) of the *Patent Act* ([see footnote b](#)), proposes to make the annexed *Regulations Amending the Patented Medicines Regulations*.

Interested persons may make representations concerning the proposed Regulations within 75 days after the date of publication of this notice. All such representations must cite the *Canada Gazette*, Part I, and the date of publication of this notice, and be addressed to Karen Reynolds, Executive Director, Office of

Pharmaceuticals Management Strategies, Strategic Policy Branch, Health Canada, 10th Floor, Brooke Claxton Building, 70 Colombine Driveway, Tunney's Pasture, Ottawa, Ontario K1A 0K9 (tel.: 613-957-1692; email: PMR-Consultations-RMB@hc-sc.gc.ca (<mailto:PMR-Consultations-RMB%40hc-sc.gc.ca>)).

Ottawa, November 23, 2017

Jurica Čapkun

Assistant Clerk of the Privy Council

Regulations Amending the Patented Medicines Regulations

Amendments

1 Section 3 of the *Patented Medicines Regulations* (see footnote 3) is amended by adding the following after subsection (3):

(3.1) Despite subsection (3), in each of the following cases, the information referred to in subsection (1) must be provided to the Board within 30 days after the day on which the Board sends a request for the patentee to provide that information:

- (a) the medicine is not a *prescription drug* as defined in section A.01.010 of the *Food and Drug Regulations*;
- (b) the medicine contains a *controlled substance* as defined in subsection 2(1) of the *Controlled Drugs and Substances Act*, the sale or provision of which does not require a prescription under that Act;
- (c) a notice of compliance has been issued in respect of the medicine on the basis of information and material contained in a submission filed under section C.08.002.1 of the *Food and Drug Regulations*; or
- (d) the medicine is for veterinary use.

2 (1) The portion of subsection 4(2) of the Regulations before paragraph (a) is replaced by the following:

(2) The information referred to in subsection (1) must be provided

(2) Subsection 4(3) of the Regulations is replaced by the following:

(3) Despite subsection (2), in each of the following cases, the information referred to in subsection (1), for each six-month period beginning on January 1 and July 1 of each year, must be provided to the Board within 30 days after the day on which the Board sends a request for the patentee to provide that information and, during the two years following the request, within 30 days after the end of each six-month period:

- (a) the medicine is not a *prescription drug* as defined in section A.01.010 of the *Food and Drug Regulations*;
- (b) the medicine contains a *controlled substance* as defined in subsection 2(1) of the *Controlled Drugs and Substances Act*, the sale or provision of which does not require a prescription under that Act;
- (c) a notice of compliance has been issued in respect of the medicine on the basis of information and material contained in a submission filed under section C.08.002.1 of the *Food and Drug*

Regulations; or

(d) the medicine is for veterinary use.

(3) Paragraphs 4(4)(a) and (b) of the Regulations are replaced by the following:

(a) in calculating the average price per package of a medicine, the actual price obtained by the patentee must be used, taking into account any adjustments that are made by the patentee or any party that directly or indirectly purchases or reimburses for the purchase of the medicine and any reduction given to any party in the form of free goods, free services, gifts or any other benefit of a like nature; and

(b) in calculating the net revenue from sales of each dosage form, strength and package size in which the medicine was sold in final dosage form, the actual revenue obtained by the patentee must be used, taking into account any adjustments that are made by the patentee or any party that directly or indirectly purchases or reimburses for the purchase of the medicine and any reduction given to any party in the form of free goods, free services, gifts or any other benefit of a like nature.

3 The Regulations are amended by adding the following after section 4:

4.1 (1) For the purposes of paragraphs 80(1)(d) and (2)(d) of the Act, the information to be provided respecting the factor referred to in paragraph 4.4(a) is every cost-utility analysis prepared by a publicly funded Canadian organization, if published, for which the outcomes are expressed as the cost per quality-adjusted life year for each indication that is the subject of the analysis.

(2) The information referred to in subsection (1) must be provided

(a) if the information is published when the medicine is first offered for sale in Canada, within 30 days after the day on which the medicine is first offered for sale in Canada; and

(b) if the information is not published when the medicine is first offered for sale in Canada, within 30 days after the day on which it is published.

(3) Despite subsection (2), in the case of a medicine that is offered for sale in Canada before January 1, 2019, the information referred to in subsection (1) must be provided

(a) if the information is published before January 1, 2019, by January 30, 2019; and

(b) if the information is not published before January 1, 2019, within 30 days after the day on which it is published.

(4) If any other analysis as described in subsection (1) is published after those referred to in subsection (1) were provided, it must be provided within 30 days after the day on which it is published.

4.2 (1) For the purposes of paragraphs 80(1)(d) and (2)(d) of the Act, the information to be provided respecting the factor referred to in paragraph 4.4(b) is the estimated maximum use of the medicine in Canada, by quantity of the medicine in final dosage form, for each dosage form and strength that are expected to be sold.

(2) The information referred to in subsection (1) must be provided within 30 days after the day on which the medicine is first offered for sale in Canada.

(3) Despite subsection (2), in the case of a medicine that is offered for sale in Canada before January 1, 2019, the most recent version of the information referred to in subsection (1) must be provided

(a) if the medicine is first offered for sale in Canada during the period beginning on January 1, 2016 and ending on December 31, 2018, by January 30, 2019; and

(b) if the information referred to in subsection (1) in respect of the medicine is not required to be provided under paragraph (a), but the information is updated

(i) during the period beginning on January 1, 2016 and ending on December 31, 2018, by January 30, 2019; or

(ii) after December 31, 2018, within 30 days after the day on which it is updated.

(4) The information provided under this section must be up to date and any modification of that information must be provided within 30 days after the day on which the modification is made.

4.3 (1) Despite subsections 4.1(2) and (3) and 4.2(2) and (3), in each of the following cases, the information referred to in subsections 4.1(1) and 4.2(1) must be provided to the Board within 30 days after the day on which the Board sends a request for the patentee to provide that information:

(a) the medicine is not a **prescription drug** as defined in section A.01.010 of the *Food and Drug Regulations*;

(b) the medicine contains a **controlled substance** as defined in subsection 2(1) of the *Controlled Drugs and Substances Act*, the sale or provision of which does not require a prescription under that Act;

(c) a notice of compliance has been issued in respect of the medicine on the basis of information and material contained in a submission filed under section C.08.002.1 of the *Food and Drug Regulations*; or

(d) the medicine is for veterinary use.

(2) The requirements of subsections 4.1(4) and 4.2(4) apply in respect of the information provided under subsection (1).

Other Factors to be Considered — Excessive Prices

4.4 For the purposes of paragraph 85(1)(e) of the Act, the other factors that the Board must take into consideration to determine whether a medicine that is sold in any market in Canada after December 31, 2018 is being or has been sold at an excessive price are the following:

(a) the pharmacoeconomic value in Canada of the medicine and that of other medicines in the same therapeutic class;

(b) the size of the market for the medicine in Canada and in countries other than Canada; and

(c) the gross domestic product in Canada and the gross domestic product per capita in Canada.

4 The schedule to the Regulations is replaced by the schedule set out in the schedule to these Regulations.

Coming into Force

5 These Regulations come into force on January 1, 2019.

SCHEDULE

(Section 4)

SCHEDULE

(Subparagraph 4(1)(f)(iii))

Australia

Australie

Belgium

Belgique

France

France

Germany

Allemagne

Italy

Italie

Japan

Japon

Netherlands

Pays-Bas

Norway

Norvège

Republic of Korea

République de Corée

Spain

Espagne

Sweden

Suède

United Kingdom

Royaume-Uni

[48-1-o]

Footnote 1

Reeves et al. “Does investment in the health sector promote or inhibit economic growth?” *Globalization and Health* (2013) 9:43.

Footnote 2

As per TBS guidelines, the discount rate used to calculate the net present value was 7%.

Footnote 3

SOR/94-688; SOR/2008-70, s.1

Footnote a

S.C. 2017, c. 6, s. 57

Footnote b

R.S., c. P-4

Government of Canada activities and initiatives

#YourBudget2018 – Advancement



(https://www.budget.gc.ca/2018/docs/themes/advancement-advancement-en.html?utm_source=CanCa&utm_medium=Activities_e&utm_content=Advancement&utm_campaign=CAbdgt18)
Advancing our shared values

#YourBudget2018 – Reconciliation



(https://www.budget.gc.ca/2018/docs/themes/reconciliation-reconciliation-en.html?utm_source=CanCa&utm_medium=%20Activities_e&utm_content=Reconciliation&utm_campaign=CAbdgt18)
Advancing reconciliation with Indigenous Peoples

#YourBudget2018 – Progress



https://www.budget.gc.ca/2018/docs/themes/progress-progres-en.html?utm_source=CanCa&utm_medium=Activities_e&utm_content=Progress&utm_campaign=CAbdgt18

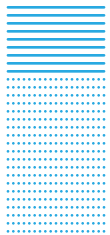
Supporting Canada's researchers to build a more innovative economy

Appendix 5.2: PMPRB Guidelines Scoping Paper



Patented
Medicine Prices
Review Board

Conseil d'examen
du prix des médicaments
brevetés



PMPRB GUIDELINES SCOPING PAPER

High Level Overview of Potential New
Framework

CGI CONSULTATION PHASE



CONTENTS

3 INTRODUCTION

4 THE NEW FRAMEWORK

5 Part I: Interim international price reference test

6 Part II: Screening

6 Part III: High priority drugs

7 Part IV: Medium and low priority drugs

7 Part V: Re-benching

8 CONCLUSION

9 NEXT STEPS

9 FURTHER INFORMATION



INTRODUCTION

This scoping paper is intended to be read in conjunction with proposed amendments to the *Patented Medicines Regulations* (“Regulations”), and accompanying Regulatory Impact Analysis Statement (RIAS), which were pre-published in the December 2nd, 2017 issue of the *Canada Gazette*, Part I. Its purpose is to provide stakeholders and interested members of the public with an outline of the PMPRB’s preliminary thoughts on how best to operationalize the proposed changes to the Regulations, through non-binding Guidelines as contemplated by s.96 of the *Patent Act*, within the context of the existing and proposed legislation and the PMPRB’s ongoing efforts at reform. It is hoped that this document will serve as a catalyst for a more informed, focussed and productive consultation process on framework modernization, with a view to having new Guidelines in place by early 2019. This document is not to be viewed as a definitive interpretation of the current or proposed legislation or of the RIAS for the proposed amendments by the PMPRB, is not the Government’s expression of policy intent or an official part of the *Canada Gazette I* (CGI) consultation, and is not intended to bind the PMPRB or the Government in the application and interpretation of legislation. The PMPRB will officially consult on a revised set of proposed Guidelines in the spring of 2018.





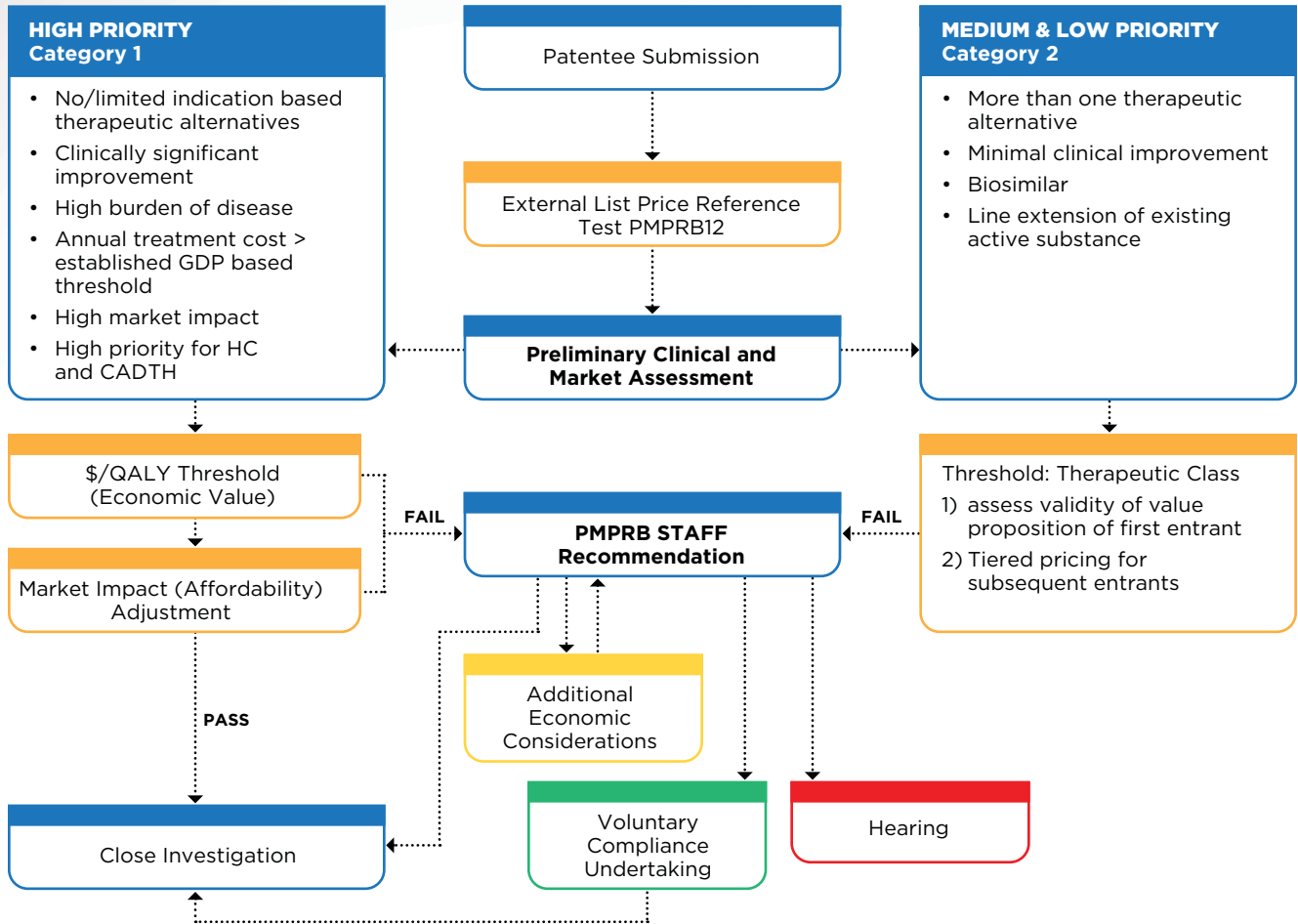
THE NEW FRAMEWORK

As an expert economic regulatory body, the PMPRB must ensure that its new framework is grounded in sound and prevailing economic theory. In conceiving the mechanics of that framework, the PMPRB was mindful of the Minister of Health's stated policy rationale for the proposed regulatory amendments and of the overarching purpose of the current and proposed legislation. The PMPRB also sought to give effect to areas of stakeholder agreement that emerged from the recent Guidelines modernization consultation. Accordingly, to the extent possible, the framework envisaged by the PMPRB employs economically-derived, bright line tests to yield meaningful ceiling prices that are foreseeable to patentees. As before, the new Guidelines are proffered as rules of general application which serve

as a mechanism for determining a rough estimate of where the line between potential non-excessive prices and potential excessive prices should be drawn by PMPRB staff. The objective of the Guidelines is to enable the calculation of a national ceiling price above which it would be unreasonable for any consumer in Canada to pay, not an ideal price for each payer based on their individual ability and willingness to pay.

While the details of the framework remain to be worked out through consultation, its basic structure can be described as a risk-based approach to pricing review that is broken down into five main parts, as illustrated in the following schematic and discussed in more detail below.

PROPOSED PRICE REVIEW SCHEMATIC*



*For discussion purposes only, not intended to bind or limit the PMPRB or the Government in the application and interpretation of legislation

Part I: Interim international price reference test

At introduction, all new drugs would first be subject to an interim price test based on the list price of a new drug in Canada against the list price in the proposed PMPRB12 basket of countries. Domestic and international list prices in today's environment of confidential discounts

and rebates represent the starting point of a price negotiation rather than a true reflection of actual price paid in the market place. In this context, the PMPRB would look at how the proposed price in Canada compares to public list prices in other markets. If the price in Canada exceeds the median of the PMPRB12, it would be considered potentially excessive.

Part II: Screening

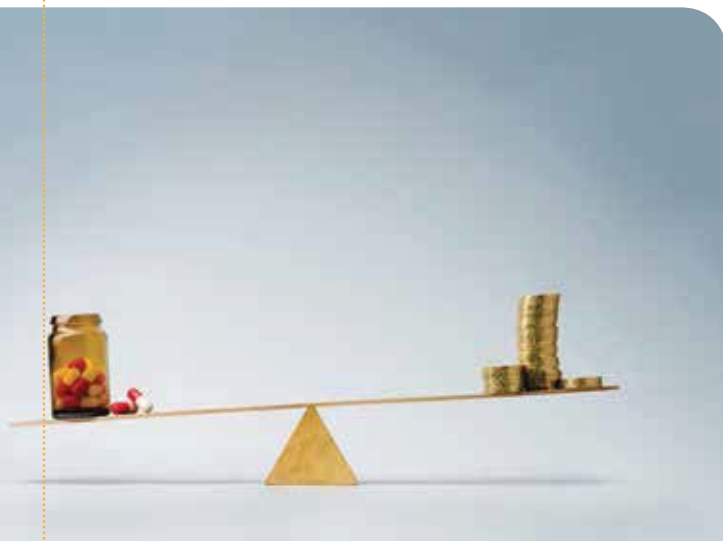
The second part of the framework consists of a screening phase which would classify new patented drugs as either high or low priority based on their anticipated impact on Canadian consumers, including individual patients and institutional payers (e.g., public and private drug plans). At this stage in the process, the PMPRB would consider whether the drug is first in class, has few or no therapeutic alternatives, provides significant therapeutic improvement over existing treatment options, is indicated for a condition that has a high prevalence in Canada, is a high cost drug (i.e. an average annual cost higher than a GDP-based threshold) or is classified as a high priority drug by other agencies/regulators in the health care system (such as the Canadian Agency for Drugs and Technologies in Health (CADTH) or Health Canada) because of unmet medical need. Drugs that appear to be high priority based on these screening factors would be subject to automatic investigation and a comprehensive review to determine whether their price is potentially excessive.

Part III: High priority drugs

Once a drug is assessed as high priority, the third part of the new framework would see the PMPRB apply a two-part test for evaluating potential excessivity¹.

The first part of the test would assess the incremental cost per quality-adjusted life year (QALY) of the drug, as determined by CADTH's health technology assessment process, against an explicit cost effectiveness threshold. The threshold would be based on the opportunity cost associated with displacing the least cost effective health technology in the Canadian health system, otherwise understood as the marginal cost of a QALY, as calculated by expert health economists and revised periodically to reflect changing market conditions. Drugs that prolong life or provide significant QALY gains could be subject to a more generous threshold, as Canadian payers have demonstrated a higher willingness to pay for these types of drugs.

The second part of the test would assess whether a drug that meets the cost effectiveness threshold should have its price further adjusted because of its expected impact on payers within the first three to five years from launch (assuming appropriate clinical utilization and no rationing of care). This test would consider the anticipated market size of the new drug against GDP growth, with the latter serving as a rough proxy for how much Canadian consumers can afford to pay for the new patented drugs that come to market on an annual basis. The test could also be used to allow a price adjustment upward in instances where a drug has a very high opportunity cost but very small market impact due to the extreme rarity of the condition it is indicated to treat.



¹ The test addresses current factors that the PMPRB must consider under s.85 of the *Patent Act* as well as the new factors that are identified in the proposed amendments to the Regulations published on December 2, 2017.

If the price fails this two-part test, the patentee would be provided with an opportunity to explain why the price of its drug is not excessive having regard to the cost of making or marketing it or such other economic factors it believes are relevant in the circumstances. Patentees would be permitted to provide confidential commercial information in support of their position, including true prices in the PMPRB12 and proposed non-transparent rebates and discounts to direct and indirect payers in Canada. If the outcome of the above process is a determination that the price of the drug is potentially excessive:

- Its public ceiling price would continue to be set by international price referencing; but
- the ceiling price resulting from the application of the two-part test would be kept confidential.

Patentees will be required to report price and revenue information to the PMPRB net of direct or indirect third party discounts or rebates. This will ensure that the PMPRB is fully informed of the actual prices for patented drugs in Canada but also enable patentees to comply with much lower ceiling prices under the new framework.

Part IV: Medium and low priority drugs

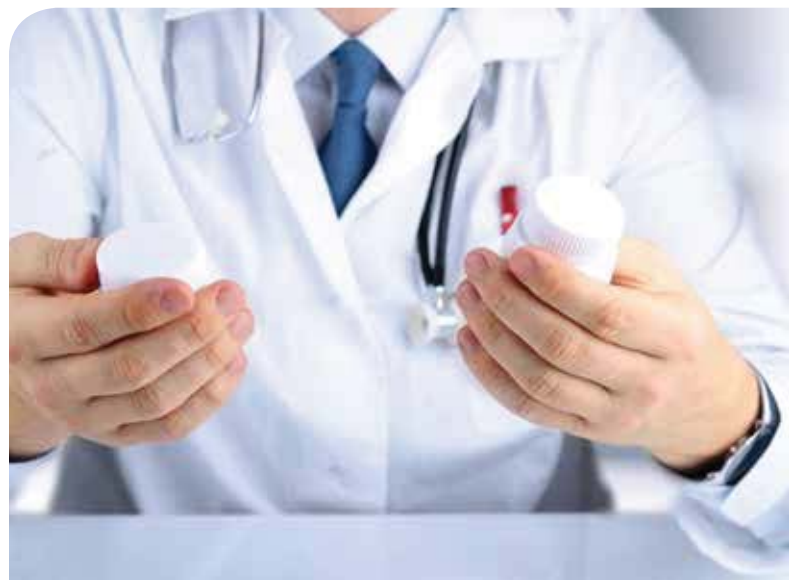
The fourth part of the new framework would apply to medium and low priority drugs. Drugs in this category would be expected to have a minimum number of therapeutic alternatives and offer little or no therapeutic improvement over the standard of care. Drugs considered to be medium priority would be subject to the same initial price test as high priority drugs, such that they would be considered potentially excessive if their public list price is above the median of public list prices in the PMPRB12 countries. For this class of drugs, the PMPRB could employ a revised therapeutic class

comparison test that requires each successive entrant to reduce its price relative to the price of the drug that preceded it. Again, patentees would be provided with the opportunity to explain why a higher price is justified based on the same economic factors that are considered relevant for high priority drugs.

Drugs categorized as low priority, because of the presence of a significant number of therapeutic alternatives in the market and/or generic competition, would not be subject to an introductory or ongoing s.85 analysis and would be investigated on a complaints basis only.

Part V: Re-benching

The fifth and final part of the new framework would involve the periodic “re-benching” of drugs to ensure that previous determinations of potential excessive pricing and/or price ceilings remain relevant in light of new indications (resulting in a change of market size) or changes in market conditions. Depending on the nature of the change, the re-benching process could result in a decrease or increase in ceiling price.





CONCLUSION

If passed in their current form, the proposed amendments would allow the PMPRB to move to a risk-based framework that scrutinizes drugs with the greatest potential for excessive pricing and takes into account both their value to, and financial impact on, consumers in the health system when setting ceiling prices. This would constitute a paradigm shift in how the PMPRB regulates patented drug prices but would not depart from or expand on its original mandate.

By explicitly requiring the PMPRB to consider the new proposed factors, policy makers have recognized that price alone does not provide sufficient context by which to evaluate excessive pricing in the current climate. Specifically, price divorced from value, cost and affordability does not capture key inputs in determining what the impact of a drug will be on payers or on total population health. These are critical considerations in an era marked by increasingly constrained health budget envelopes, an aging population and an ever increasing number of drugs with annual average treatment costs in the hundreds of thousands of dollars.

It should be emphasized that the above described framework is only notional at this stage and may change as a result of any differences between the proposed amendments and the final Regulations or in response to stakeholder feedback from PMPRB-led consultations on Guideline reform.



NEXT STEPS

In the coming weeks, Health Canada and the PMPRB will be hosting multi-stakeholder webinars where the department will address the proposed regulatory amendments and the PMPRB will address the changes discussed in this scoping paper. The PMPRB will also be making Guideline reform the focus of its upcoming annual outreach sessions for patentees to be held in January of 2018. It is expected that a first draft of the PMPRB's new Guidelines will be made public in the spring of 2018, with technical roundtables to be scheduled shortly thereafter. However, at this stage of the process, the PMPRB is specifically encouraging stakeholders to reflect on the following questions in order to prepare for upcoming consultations on a revised set of proposed Guidelines:

1. What considerations should PMPRB use in screening drugs for high priority?
2. To what extent should low priority drugs be scrutinized?
3. How should a cost effectiveness threshold be established?
4. Should the application of a threshold be subject to further adjustment depending on market size considerations?
5. How should re-benching work and when should it occur (and to what drugs)?
6. What price tests should the PMPRB apply to the new PMPRB12?
7. How should the PMPRB make use of confidential third party pricing information?

FURTHER INFORMATION

Questions or clarifications on the content of this document can be submitted by email, letter mail or fax to:

Patented Medicine Prices Review Board

Box L40, 333 Laurier Avenue West, Suite 1400

Ottawa, Ontario K1P 1C1

Fax: 613-952-7626

E-mail: PMPRB.Consultations.CEPMB@pmprb-cepmb.gc.ca

Appendix 5.3: PMPRB Framework Modernization Presentation



Patented
Medicine Prices
Review Board

Conseil d'examen
du prix des médicaments
brevetés

PMPRB Framework Modernization

*Presentation to Working Group
July 26, 2018*

Canada

Outline

- Summary of proposed regulatory amendments
- Overview of proposed New Guidelines framework
- Steering Committee Mandate

We've been consulting since June 2016

PMPRB
Discussion paper on
Guideline reform



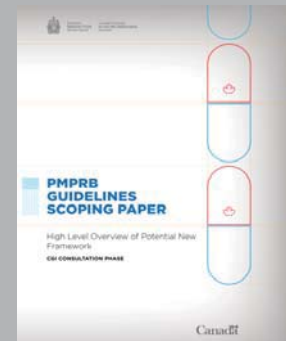
Health Canada
pre-consultation
on regulatory
amendments



Health Canada
Gazette 1



PMPRB
Guidelines
scoping paper



3

The Current Regime

New patented drugs are assessed for level of therapeutic benefit relative to existing therapies and assigned a ceiling price that is based on either:

1. The median international price;
2. The highest price in the domestic therapeutic class, or;
3. Some combination of the two.

After entering the market, the price of a drug can increase in keeping with CPI but never to the point of becoming highest of the **PMPRB7**.

Where PMPRB staff and a patentee disagree about whether a new or existing drug is excessively priced, a hearing may be held before PMPRB Board Members.

If Members decide a drug is excessively priced, they can order the patentee to reduce its price and/or pay back excess revenues.

4

Main problems with current framework

- Our basket of comparators – the **PMPRB7** - is made up of premium priced countries and includes the US, an international outlier.
- It is based on publicly available list prices, which are increasingly divorced from the true price net of confidential rebates/discounts.
- For many high cost drugs, the only factor the PMPRB can consider in setting the ceiling price is its public list price in the PMPRB7
- All drugs are subject to the same level of regulatory scrutiny, regardless of price/cost and market dynamics.
- Our only absolute ceiling for existing drugs is highest international price.

5

Framework modernization

The three key changes being proposed will allow PMPRB to:

1. Compare prices to basket of countries that align more closely with Canadian context and priorities;
2. See what actual prices are being charged in Canada, so that whole regime isn't based on false values from the outset;
3. Consider the value of a drug and its potential impact on pharmaceutical spending in the price review process.

6

Changing the basket of countries

Currently, the PMPRB checks the prices of patented drugs in 7 comparator countries to set the ceiling price of a new drug in Canada

The Government is proposing to include additional comparator countries and to drop the 2 outliers:

- United States whose drug prices are three times higher than other countries
- Switzerland whose GDP per capita is almost double that of Canada

PMPRB-7 (existing basket)	
Country (¹ retained in new basket)	CDN Price Ratio
France ¹	0.78
Germany ¹	1.00
Italy ¹	0.83
Switzerland	1.06
Sweden ¹	0.89
United Kingdom ¹	0.84
United States	2.91

PMPRB-12 (new basket)			
Country (² added to new basket)	CDN Price Ratio	Country (² added to new basket)	CDN Price Ratio
Australia ²	0.78	Norway ²	0.75
Belgium ²	0.80	South Korea ²	0.54
France	0.78	Spain ²	0.80
Germany	1.00	Sweden	0.89
Italy	0.83	United Kingdom	0.84
Japan ²	0.92		
Netherlands ²	0.79		

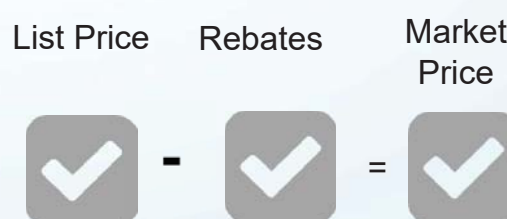
7

Regulating true prices

- When the PMPRB was created, actual prices paid in the market matched the public list prices
- Now, as a result of significant discounts and rebates to third-party payers, actual prices paid in the market are significantly lower than list prices
- Without access to this information, the PMPRB is unable to set ceiling prices that are actually meaningful to payers.

Current


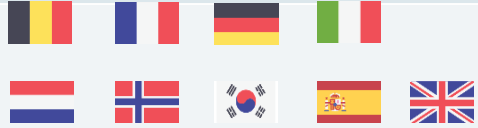
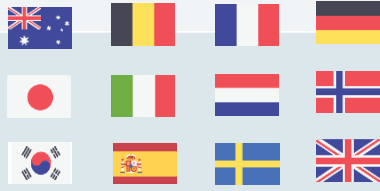
Proposed



8

New pricing factors

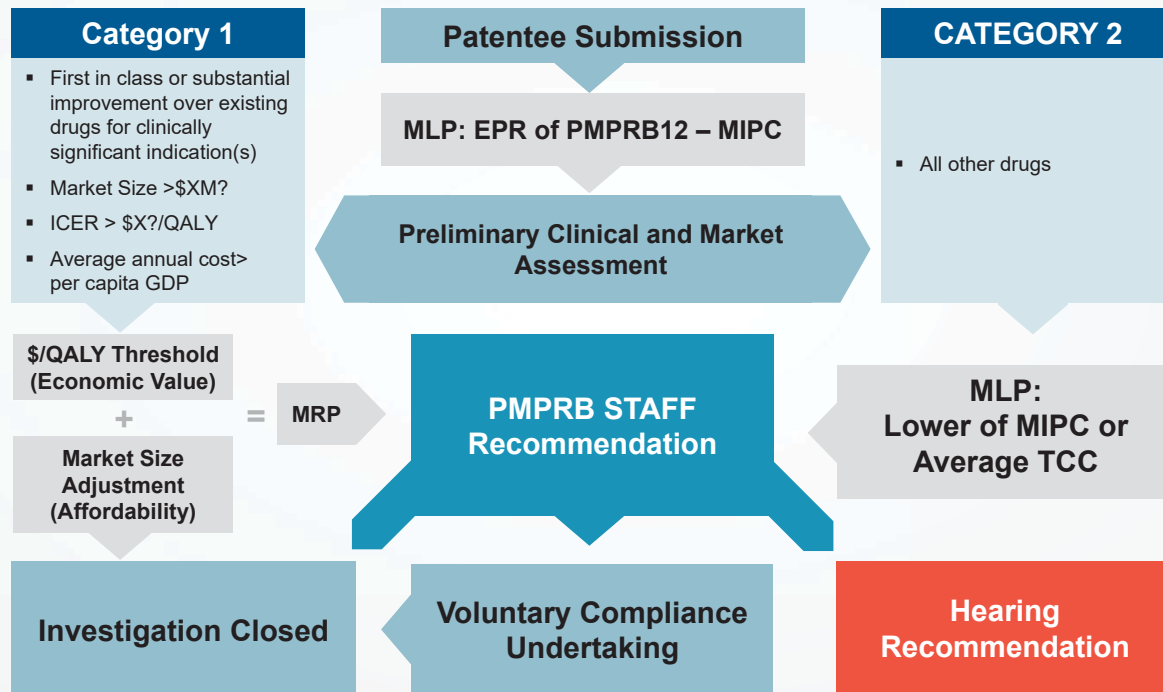
Most other regulators look at additional factors beyond simply comparing prices paid in other countries, such as value for money and the size of the market

Factor	Description	Comparator Countries Using the Factor
Value for Money	<ul style="list-style-type: none"> Comparison of the costs and benefits of a drug to patients and the healthcare system If paying for the drug would result in a net loss in total population health because it costs substantially more than existing drugs which provide the same or greater amount of health benefit, the price must come down 	
Size of the market	<ul style="list-style-type: none"> Consideration of ability-to-pay in Canada and the flexibility to re-assess subsequent changes in market size So, if a drug serves a significant number of patients, its high cost could make it unaffordable and limit access to a subset of the patient population 	
Canadian GDP and GDP per capita	<ul style="list-style-type: none"> Growth in GDP can be used as an indicator of the country's ability to pay while per capita GDP is a proxy for buying power at the level of the individual So, if the price exceeds the ability of Canada (measured by GDP) or Canadians (measured by GDP per capita) to pay for the drug, it may suggest that the drug price is excessive 	

Overview of new Guidelines framework

- A risk-based approach to price regulation that considers value and affordability, in addition to list prices in other like-minded countries.
- Basic structure can be broken down into 5 parts:
 - Part I: 'Maximum List Price' (MLP) for all new drugs at introduction based on median of PMPRB12 (MIPC)
 - Part II: Screening of drugs into high priority (Category 1) or low priority (Category 2)
 - Part III: 'Maximum Rebated Price' (MRP) for Category 1 drugs based on new pharmacoeconomic, market size and GDP factors
 - Part IV: Lower of MIPC and average of Therapeutic Class (ATCC) for Category 2 drugs
 - Part V: Re-benching
- The MLP will be a transparent ceiling based on public list prices but the MRP, which applies to Category 1 drugs only, will be confidential.
- To comply with the MRP, patentees of Category 1 drugs will be required to submit information on undisclosed rebates to third parties.

Proposed PRICE Review Schematic



Old vs new regime...

Rule	How The Current Regime Works	How The Updated Regime Would Work
How international prices affect maximum prices in Canada	A new and improved drug cannot be priced higher than the median price of that same drug in the PMPRB7	All new drugs cannot be priced higher than the median price of that same drug in the PMPRB12
How domestic prices affect maximum prices in Canada	A new drug that isn't an improvement over existing drugs cannot be priced higher than the highest priced existing comparator drug in Canada	A new drug that isn't an improvement over existing drugs cannot be priced higher than the lower of the average price of existing comparator drugs in Canada and the median of the PMPRB12
How inflation affects maximum prices in Canada	The price of a drug can increase every year with inflation. However, if a drug's price decreases in one year, its ceiling price the next year will be constrained by that decrease in price.	The ceiling price of a new drug is fixed at introduction. Prices can vary freely below this level in subsequent years.
Changes to the maximum ceiling price after a new drug enters Canada	Once a new drug is given its ceiling price, it can only change through inflation or if the drug company voluntarily lowers it.	The maximum price may be rebenchmarked after a few years based on specific changes in market conditions.

Old vs new regime (continued)

Rule	How The Current Regime Works	How The Updated Regime Would Work
Pharmacoeconomics	How much a drug costs for the amount of benefit it provides (e.g., \$100 a pill for a year of healthy life) is not considered by the PMPRB in setting a maximum price	The cost-effectiveness of Category 1 drugs in terms of cost per quality-adjusted life year (QALY) is assessed against an evidence based threshold
Market size and GDP*	The total amount of money available to be spent on new drugs every year is not considered by the PMPRB in setting a maximum price	The market size of a new drug is a function of how much it costs and how many patients will need it. Drugs that are expected to have a significant market size and impact on the healthcare system will have a lower ceiling price to deter rationing.

*Each year, the amount of money available to be spent on new drugs depends on total spending on drugs the year before and how much the economy is growing. For example, if Canada spent \$1000 on drugs in 2018 and its economy grew by 2%, it would have \$20 more to spend on the new drugs that come to market in 2019 (for a total of \$1020)

Part 1: Median international price test (MIPC)

- All new drugs are assigned a Maximum List Price (MLP) based on the median of the PMPRB 12 (MIPC).
- IMS will be used to verify international list prices.
- Category 1 drugs will be given both an MLP based on the MIPC and a Maximum Rebated Price (MRP)
- All other drugs will be deemed Category 2 and have an MLP based on the lower of the MIPC and the average of the domestic therapeutic class (ATCC).
- No Category 2 drug will be given an MLP that is lower than the lowest price country in the PMPRB12 (LIPC floor).

Part II: Screening

- Drugs will be screened into Category 1 if they are:
 1. First in class or substantial improvement over existing therapy
 2. Expected to have sales in excess of a \$X million/year market size threshold
 3. Above a \$X/QALY threshold for clinically significant indications
 4. Have an average annual treatment cost above per capita GDP.

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Part III: MRP for Category 1 drugs

- Step 1: application of pharmacoeconomic factor
 - Empirical work undertaken by Karl Claxton at the University of York suggests a \$30K/QALY opportunity cost threshold for Canada.
 - Question whether and to what extent that estimate should be taken into account in at the screening phase to determine whether a drug should go in Category 1 or Category 2.
 - Category 1 drugs will then be subject to a baseline maximum value-based price ceiling of \$X/QALY, for reasons of practicality and efficiency.
 - Drugs that meet certain clinical characteristics (e.g., high burden of disease or significant absolute gain in QALY) may be subject to a higher \$/QALY ceiling.

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Part III: MRP for Category 1 drugs (continued)

- Step 2: application of market size and GDP factors
 - A Category 1 drug that meets the applicable \$/QALY ceiling may still face an adjustment in price if the application of the market size and GDP factors raise affordability concerns.
 - Using new drug contribution to GDP and GDP growth over the last five years, the PMPRB is estimating a threshold of \$XM per new drug.
 - New Category 1 drugs with an estimated market size that exceeds this threshold within any of its first five years of sale will require further price adjustments.
 - The adjustment would see the MRP reduced by a certain percentage discount which would increase as the expected market size increases (see next slide).
 - The market size threshold would also increase annually based on GDP growth and/or CPI.

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Application of new factors to Category 1 drugs – potential thresholds

Type of review	\$/QALY target to set MRP	Market impact adjustment
Baseline New Drug (market size up to \$20M)	\$60K	N/A
“Premium” New Drug (e.g. high burden, EDRD, significant absolute QALY gain)	\$90K to \$150K	N/A
High Impact New Drug (market size over \$20M)	\$60K	10% reduction on MRP for each additional \$10M market size (to 50% maximum)

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Part IV: MLP for Category 2 drugs

- As mentioned, Category 2 drugs have an MLP based on the lower of the MIPC and the average of the domestic therapeutic class (ATCC).
- However, no Category 2 drug will be given an MLP that is lower than the lowest price country in the PMPRB12 (LIPC floor).

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Part V: Re-benching

- All new drugs will be given an interim MLP of 3 years or until the drug is sold in 7 countries, whichever comes first.
- MLP is then frozen, as is MRP, unless re-benching is triggered by one of the following criteria:
 - Approval of a new indication
 - Sales in excess of expected market size
 - New evidence on cost-effectiveness (e.g. CADTH therapeutic class review or lifting of HC conditions on NOC)
 - Significant changes in international prices (eg. $MIPC < MIPC$ at intro by more than 25%)
- Patentees may apply for a re-benching with evidence of increased cost-effectiveness, smaller market, or a significant increase in CPI

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How compliance with new price ceilings will be assessed

- Price reviews will be conducted for the following customer classes:
 - National Retail – list price assessed against MLP
 - National Private Payer – average transaction price (ATP) assessed against MRP
 - Provincial Public Payer – ATP assessed against MRP in each market
- ATPs are calculated net of all discounts to determine compliance with confidential MRP.
- Category 2 drugs will be assessed against MLP.

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How pricing complaints will be managed

Complaints received by the PMPRB will trigger an investigation, during which the PMPRB will assess whether:

1. a drug is in compliance with the Guidelines; and
2. whether circumstances in the market have changed to warrant a rebenching/reclassification.

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Application of new Guidelines to existing drugs

- Existing drugs will be given an interim price ceiling based on the MIPC of the PMPRB12.
- An existing drug will only be classified as Category 1 if it fails a \$X/QALY screen for any indication (would be higher than screen used for new drugs, for administrative and operational reasons).
- Existing drugs that are screened into Category 1 will be prioritized for re-benching.
- Category 2 drugs will be re-benched later unless a complaint is received.
- All drugs within a therapeutic class will be assessed at the same time for the purposes of the ATCC test.
- Patentees will be advised in advance of re-benching and given two reporting periods to come into compliance.

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PMPRB Guidelines Modernization Steering Committee

- The Steering Committee is being asked to provide targeted stakeholder feedback on key features of a new Guidelines framework which will serve the following dual objectives:
 1. Operationalize amendments to the Patented Medicines Regulations designed to lower patented drug prices; and,
 2. Support a risk-based approach to regulating drug prices that simplifies and streamlines compliance for patentees.
- In deliberating on the above, the Steering Committee should seek to strike a balance between the following guiding principles:
 - Sustainability
 - Predictability
 - Consistency
 - Functionality
 - Fairness
- The Steering Committee will be informed by the technical Working Group (the “**Working Group**”).

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Suggested questions for Steering Committee

- Is the proposed division and treatment of Category 1 and Category 2 drugs a reasonable risk-based regulatory approach?
- Is an MLP based on the median of the PMPRB12 (MIPC) for all drugs reasonable?
- Should exceptions be made to the MLP-MIPC test and, if so, when and why?
- Should there be a price floor for Category 2 drugs based on LIPC?
- Should further drug categories exist with different treatment modalities from those proposed?
- Should more or less criteria be considered in screening a drug as higher risk and, where should the line be drawn with respect to the criteria?
- Should the pharmacoeconomic, market size and GDP factors apply both as screens and thresholds?
- Should Category 2 drugs be scrutinized more or less than proposed?
- Should the cost effectiveness threshold for Category 1 drugs vary?
- Should a Category 1 drug ever have more than one MRP?
- Are there economic considerations that would support a higher MRP for some Category 1 drugs than would result from the proposed application of the new factors?
- How often and in what circumstances should a drug be rebenchmarked?
- Should confidential third party pricing information only be used for compliance purposes?
- Is there a better way to deal with existing drugs under the new framework?
- Are there opportunities to further reduce regulatory burden while respecting the dual objectives?

Appendix 5.4: PMPRB Short Primer



PATENTED MEDICINE PRICING REVIEW BOARD

Prepared for the Working Groups on Guideline Reforms

July 2018

The following short description is intended to address questions raised during the technical working group meeting about the PMPRB's mandate and role.

Prior to 1987, the Canadian Patent Act ("Act") allowed generic drug manufacturers to obtain compulsory licences to produce generic versions of patented brand name drugs at any time during the patent term. In addition, the Act only allowed for the patenting of processes to make medicines, but not the medicines themselves.

In 1987, the *Act* was substantially amended to reduce the availability of compulsory licences to generic manufacturers and to allow patents for the medicine themselves. These changes gave rise to a concern that patentees would abuse their newfound patent rights by charging prices above "reasonable" levels. To address this concern, the Act was further amended to create the PMPRB. All of these amendments were made to the Act through Bill C-22.

In introducing Bill C-22 in Parliament, the responsible Minister, the Hon. Harvie Andre, had the following to say regarding the dual intentions underlying the legislation:

In essence, the amendments I propose in Bill C-22 will create a climate favourable to new investment in research and development in Canada by giving patent holding firms in Canada a guaranteed period of protection. These changes will also ensure consumer protection by creating a new prices review board to monitor drug prices...¹

There is the question of consumer protection. What good would come of it if we had all kinds of new drugs and no one could afford them? If the sick and elderly could not get access to the drugs, what good would come of it? ...²

I hereby submit that anybody who takes an objective view of what we are proposing will see that we have in place enormous checks and balances to ensure that consumer prices of drugs remain reasonable...³

Thus, while the purpose of stronger patent rights for pharmaceutical manufacturers is to incent innovation in Canada, the purpose of the PMPRB is to act as an effective check on these rights by

¹ House of Commons Debates, 33rd Parliament, 2nd Session, Vol. 1, page 1369, Hon. Harvie Andre (Minister of Consumer and Corporate Affairs).

² House of Commons Debates, 33rd Parliament, 2nd Session, Vol. 1, page 1371, Hon. Harvie Andre (Minister of Consumer and Corporate Affairs).

³ House of Commons Debates, 33rd Parliament, 2nd Session, Vol. 1, page 1373, Hon. Harvie Andre (Minister of Consumer and Corporate Affairs).

ensuring that patentees do not charge excessive prices during the statutory monopoly period. The consumer protection the PMPRB provides extends to all Canadian purchasers of medicines, be they government, insurers, wholesalers or private individuals.

In a statutory monopoly situation, a seller has the ability to limit competition and thus can set a higher price than would otherwise exist, possibly to excessive levels. This risk of excessive pricing is exacerbated where demand for the product is high and there are few, if any, substitutes. In the pharmaceutical realm, this situation is most likely for patented medicines that are the first effective treatment of their kind for life threatening ailments. The PMPRB's existence as the only sector-specific regulator under the Act is attributable to this fact and a recognition by policy makers that the unfettered monopoly pricing of patented medicines is not in the public interest.

In 1993, the Act was amended again to eliminate the special compulsory licencing regime that had applied only to patented medicines and, as an offsetting measure, to provide the PMPRB with additional remedial powers in dealing with cases of excessively priced patented medicines. In speaking to the latter set of amendments, the sponsoring Minister, the Hon. Pierre Blais, explained to Parliament that their purpose was "to strengthen consumer protection, so that consumers can continue to obtain patented medicines at reasonable prices" and to "assure Canadian consumers, of reasonable prices, like those they have had since 1987."

The scope of the PMPRB's powers reside in sections 83 and 85 of the Act. Section 83 enables the Board to order a patentee to lower its maximum price where it is found to be "excessive".

Where the Board finds that a patentee of an invention pertaining to a medicine is selling the medicine in any market in Canada at a price that, in the Board's opinion, is excessive, the Board may, by order, direct the patentee to cause the maximum price at which the patentee sells the medicine in that market to be reduced to such level as the Board considers not to be excessive

The Act does not define what an "excessive" price is, and instead directs the PMPRB to consider the following factors at section 85 in making that determination:

- the prices at which the medicine has been sold in the relevant market;
- the prices at which other medicines in the same therapeutic class have been sold in the relevant market;
- the prices at which the medicine and other medicines in the same therapeutic class have been sold in countries other than Canada;
- changes in the Consumer Price Index;
- *[proposed factor] the size of the market for the medicine in Canada and in countries other than Canada;*
- *[proposed factor] the gross domestic product in Canada and the gross domestic product per capita in Canada;*
- *[proposed factor] the pharmacoeconomic value in Canada of the medicine and that of other medicines in the same therapeutic class*

While the PMPRB can order price reductions following a hearing, it also issues Guidelines that outline how it monitors the prices of patented medicines to identify whether the price of any particular medicine should be considered potentially excessive and the subject of a hearing. The Guidelines are not binding, but they provide guidance on patentee pricing behaviour and adherence with the Guidelines reduces the likelihood that a patentee may find itself in a hearing before the Board.

Although it is part of the Health Portfolio, the PMPRB as a whole maintains an arm's length relationship with other entities including the Minister of Health and stakeholders. In other words, the PMPRB conducts its price monitoring and decides hearings independently from those entities. For example, while complaints from third parties may initiate an investigation under the Guidelines, the complainant has no part or role in the actual investigation or its resolution.

The PMPRB has no mandate or policy tools to incent innovation in Canada, cannot bar a patented medicine from being marketed in Canada; makes no decisions or recommendations regarding the approval of medicines for safety, efficacy and quality; and makes no decisions or recommendations regarding the listing or reimbursement of medicines in drug plans.

The Government believes that the PMPRB's current regulatory framework does not provide it with adequate tools to effectively protect Canadians from excessive prices, or for optimal identification of maximum prices in today's pharmaceutical environment. That is why Health Canada is advancing the proposed regulatory amendments, including new s.85 factors in the form of pharmacoeconomic value, market size and GDP.

Appendix 6: Case Studies



Patented
Medicine Prices
Review Board

Conseil d'examen
du prix des médicaments
brevetés

Guideline Modernization Case Studies



December 13, 2018

Canada 

Summary of Cases

	Treatment cost (annual or full regimen)	Potential treatment population (annual)	Potential annual revenues	Profile	Potential disease area
Case 1	\$1K	500,000	\$500M	Treats a chronic condition One approved indication Has comparators Very large treatment population	Diabetes, Mental health disorders
Case 2	\$7K	100,000	\$700M	Treats a chronic condition One approved indication Substantial therapeutic benefit, no approved comparators Large treatment population each year	AMD
Case 3	\$20K	103,000	\$2B	Substantial therapeutic benefit to a less common chronic condition with a small treatment population Moderate therapeutic benefit to a more common chronic condition with a large treatment population	DMARDs
Case 4	\$50K	3,000	\$150M	One approved indication for 2 nd line treatment of cancer Several therapeutic alternatives exist Small treatment population	Oncology
Case 5	\$50K	200,000 (31,000)	\$1.5B	Provides cure for a serious condition Large treatment population If no rationing, all could be treated in 7 years	Hep C
Case 6	\$300K	1,000	\$300M	Rare disease drug with one indication Limited clinical significance Small treatment population, high severity of illness, unmet need	EDRD

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Acronyms

HIPC – Highest international price comparison

MIPC – Median international price comparison

LIPC – Lowest international price comparison

TCC – Therapeutic class comparison

MLP – Maximum list price

MAPP – Maximum average potential price

MRP – Maximum rebated price

NEAP – Non-excessive average price

HTA – Health Technology Assessment

QALY – Quality-adjusted life year gained

ICER – Incremental cost-effectiveness ratio

PV – pharmacoeconomic value

\$/QALY – cost per quality adjusted life years gained

RWE – Real world evidence

Case 1 – Large population, therapeutic comparators

- Treats a chronic condition
- Has therapeutic comparators
- One approved indication by Health Canada (HC)
- Very large potential treatment population
 - Possible indications: diabetes, mental health disorders, etc.
- Annual treatment cost (list price): \$1,000*
- Population with the condition: 500,000
- Potential annual revenues based on the total treatment population: \$500M
- Category 1 due to market size

* Assumed a once-a-year dose for ease of calculations.

Case 1 – Application of the Proposed Guidelines

Factor	Intro Period	End of Year 1	End of Year 2	End of Year 3*	End of Year 4	End of Year 5	End of Year 6
MLP (set by MIPC)	\$800	\$785	\$780	\$750	\$750	\$750	\$750
PV Threshold Price**	N/A	\$640	N/A	N/A	N/A	N/A	N/A
Revenue at PV Price	N/A	\$33M	\$50M	\$68M	\$75M	\$81M	\$91M
Market Size Adjustment ***	N/A	N/A	10%	30%	N/A	N/A	N/A
MRP	N/A	\$640	\$627	\$581	\$581	\$581	\$581
Total revenue at MRP	N/A	\$33M	\$49M	\$61M	\$68M	\$74M	\$82M

*MLP/MRP frozen.

**CADTH estimated ICER is \$100K. PV threshold used is \$60,000/QALY.

***A progressive discount applies to the total annual drug cost (revenue) at the cost-effective price, where each successive \$10M above \$40M is discounted by an additional 10%, up to a maximum of 50%. This \$40M market size threshold has been used for demonstration purposes only.

Case 1 – Current vs New Proposed Guidelines

Original ex-factory Price	\$1,000	
	<i>Current Guidelines</i>	<i>Proposed Guidelines</i>
Price Ceiling	\$1900 (assume top of TCC > MIPC)	Ex-factory price ceiling (MLP): \$750 Rebated price ceiling (MRP): (frozen at year 3): \$581
Tests used to set the Ceiling	Midpoint of top of TCC and MIPC (moderate improvement)	MLP: MIPC MRP: 30% adjustment to PV price
Ceiling percent reduction from original price	none	MLP: 25% MRP: 42%
Compliance assessment made against	ATP (rebated price including free goods, but not PLAs)	MLP: ex-factory price MRP: ATP where rebates include PLAs

Case 2 – Large population, no therapeutic alternatives

- Treats a chronic condition
- One clinically significant approved indication
- No therapeutic alternatives
- Large treatment population
 - Potential disease areas: age-related macular degeneration (AMD).
- Annual treatment cost (list price): \$7K
- Population with the condition: 100K in any given year
- Potential annual revenues based on the total treatment population: \$700M
- Category 1 based on projected market size, no therapeutic alternatives

Case 2 –Application of the Proposed Guidelines

Factor	Intro Period	End of Year 1	End of Year 2	End of Year 3*	End of Year 4	End of Year 5
MLP (set by MIPC)	\$6.7K	\$6.3K	\$6.0K	\$6.0K	\$6.0K	\$6.0K
PV Threshold Price**	N/A	\$3,490	N/A	N/A	N/A	N/A
Revenue at PV Price	N/A	\$67M	\$97M	\$125M	\$80M	\$97M
Market Size Adjustment	N/A	30%	50%	N/A	N/A	N/A
MRP	N/A	\$3,050	\$2,525	\$2,525	\$2,525	\$2,525
Total Revenue at MRP	N/A	\$62M	\$79M	\$92M	\$70M	\$79M

*MLP/MRP frozen at year 3.

**CADTH estimated ICER is \$100K. PV threshold used is \$60K/QALY.

Case 2 – Current vs New Proposed Guidelines

Original ex-factory Price	\$7,000	
	<i>Current Guidelines</i>	<i>Proposed Guidelines</i>
Price Ceiling	\$6000	Ex-factory price ceiling (MLP): \$6000 Rebated price ceiling (MRP): \$2525
Tests used to set the Ceiling	MIPC	MLP: MIPC MRP: cost effectiveness adjusted for market size
Ceiling percent reduction from original price	14%	MLP: 14% MRP: 64%
Compliance assessment made against	ATP (rebated price, rebates include free goods, but not PLAs)	MLP: ex-factory price MRP: ATP where rebates include PLAs

Case 3 – Two indications with different therapeutic benefits and prevalence rates

- Treats 2 chronic conditions
 - Condition 1 (first indication): estimated 3,000 people in Canada, first in class, brings significant therapeutic improvement over standard of care
 - Condition 2 (subsequent indication): Estimated 100,000 people in Canada, Therapeutic alternatives available, brings slight or no therapeutic improvement
- No therapeutic alternatives for condition 1, therapeutic alternatives for condition 2
- Annual treatment cost: \$20K
- Potential annual revenues based on the total treatment population: \$2B
- Category 1 based on projected market size.

Case 3 – Application of the Proposed Guidelines (first indication)

Factor	Intro Period	End of Year 1	End of Year 2*	End of Year 3**	End of Year 4	End of Year 5	End of Year 6
MLP (set by MIPC)	\$19K	\$18K	\$17K	\$17K	\$17K	\$17K	\$17K
PV Threshold Price ***	N/A	\$9,975	N/A	N/A	N/A	N/A	N/A
Revenue at PV Price	N/A	\$99M	\$143M	\$195M	\$249M	\$304M	\$362M
Market Size Adjustment	N/A	40%	50%	50%	N/A	N/A	N/A
MRP	N/A	\$7,580	\$6,329	\$5,835	\$5,835	\$5,835	\$5,835
Revenue at MRP	N/A	\$80M	\$102M	\$128M	\$163M	\$199M	\$237M

*MLP frozen based on 7 countries.

**MRP frozen after 3 years.

*** ICER threshold used is \$60K/QALY.

Case 3 – Application of the Proposed Guidelines (second indication)

Several therapeutic resulting in median TCC \$6,000; LIPC = \$14K

Factor	Intro Period	End of Year 1	End of Year 2*	End of Year 3**	End of Year 4	End of Year 5	End of Year 6
MIPC	\$19K	\$18K	\$17K	\$17K	\$17K	\$17K	\$17K
PV Threshold Price ***	N/A	N/A	N/A	N/A	N/A	N/A	N/A
MLP=higher of LIPC and median TCC	\$14K	\$13	\$12.5	\$12.5	\$12.5	\$12.5	\$12.5
Revenue at MLP	\$72M	\$137M	\$201M	\$237M	\$348M	\$426M	\$507M
Market Size Adjustment	N/A	20%	30%	40%	N/A	N/A	N/A
MRP	\$6,000	\$5,627	\$4,680	\$3,712	\$3,712	\$3,712	\$3,712
Revenue at MRP	\$31M	\$59M	\$75M	\$81M	\$103M	\$126M	\$151M

Case 3 –Current vs New Proposed Guidelines

Original ex-factory Price	\$20,000	
	Current Guidelines	Proposed Guidelines
Price Ceiling Indication 1	\$19,000	Ex-factory price ceiling (MLP): \$17,000 Rebated price ceiling (MRP): \$7,580
Price Ceiling Indication 2	\$19,000	Ex-factory price ceiling (MLP): \$14,000 Rebated Price ceiling (MRP): \$5,627
Tests used to set the Ceiling	MIPC	MLP: MIPC for condition 1 LIPC for condition 2 MRP: lower of MLP or med TCC adjusted for market size for condition 2
Ceiling percent reduction from original price	None	MLP: 10%; 26% MRP: 60%; 70%
Compliance assessment made against	ATP (rebated price, rebates include free goods, but not PLAs)	MLP: ex-factory price MRP: ATP where rebates include PLAs

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Case 4 – 2nd line oncology medicine

- One clinically significant approved indication
- Several therapeutic alternatives exist
- Low 5-year survival rates
- Small treatment population: 3,000
- Annual treatment cost: \$50,000
- Potential annual revenues based on the total treatment population: \$150M
- Category 1 based on projected market size, annual treatment cost above GDP/capita

Case 4 – Application of the Proposed Guidelines

Factor	Intro Period	End of Year 1	End of Year 2	End of Year 3*	End of Year 4	End of Year 5	End of Year 6
MLP (set by MIPC)	\$47.5K	\$45K	\$42.5K	\$40K	\$40K	\$40K	\$40K
PV Threshold Price**	N/A	\$25K	N/A	N/A	N/A	N/A	N/A
Revenue at PV Price	N/A	\$10M	\$15M	\$19M	\$25M	\$30M	\$36M
Market Size Adjustment***	N/A	MIPC	MIPC	MIPC	MIPC	MIPC	MIPC
MRP	N/A	\$45K	\$42.5K	\$40K	\$40K	\$40K	\$40K
Revenue at MRP	N/A	\$14M	\$20M	\$26M	\$33M	\$40M	\$47M

*MLP/MRP frozen.

**CADTH estimated ICER is \$250K. PV threshold used is \$60K/QALY.

***Positive market size adjustment owing to small market size – lower of MIPC, 2xPV Threshold price

Case 4 – Current vs New Proposed Guidelines

Original ex-factory Price	\$50,000	
	<i>Current Guidelines</i>	<i>Proposed Guidelines</i>
Price Ceiling	\$45K (assume top of TCC < MIPC)	Ex-factory price ceiling (MLP): \$40K Rebated price ceiling (MRP): (frozen at year 3): \$40K
Tests used to set the Ceiling	Midpoint of top of TCC and MIPC (moderate improvement)	MLP: MIPC MRP: Lower of MIPC, 2xPV threshold price
Ceiling percent reduction from original price	10%	MLP: 20% MRP: 20%
Compliance assessment made against	ATP (rebated price including free goods, but not PLAs)	MLP: ex-factory price MRP: ATP where rebates include PLAs

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Case 5 – Curable condition, large treatment population

- Provides cure for a common and serious condition
- Large treatment population: estimated 200,000 Canadians are living with the condition
 - All could be treated in seven years assuming no rationing
- As of 2018, the health care system cost associated with the condition is estimated at \$10 billion annually.
- Annual treatment cost of \$50K (based on the manufacturer's suggested list price)
- Potential annual revenues based on the total treatment population: \$1.5B
- Category 1 based on projected market size, annual treatment cost above GDP/capita

Case 5 – Application of the Proposed Guidelines

Factor	Intro Period	End of Year 1	End of Year 2*	End of Year 3**	End of Year 4	End of Year 5	End of Year 6
MLP (set by MIPC)	\$48K	\$45K	\$43K	\$43K	\$43K	\$43K	\$43K
PV Threshold Price***	N/A	\$50K	N/A	N/A	N/A	N/A	N/A
Revenue at PV Price	N/A	\$1.5B	\$1.5B	\$1.5B	\$1.5B	\$1.5B	\$1.5B
Market Size Adjustment****	N/A	50%	50%	50%	50%	50%	50%
MRP	N/A	\$25K	\$24K	\$23K	\$23K	\$23K	\$23K
Total revenue at MRP	N/A	\$770M	\$740M	\$708M	\$708M	\$708M	\$708M

*MLP frozen based on 7 countries.

**MRP frozen.

***CADTH estimated ICER is \$50K, below PMPRB PV threshold

****Maximum market size adjustment of 50%. Assuming competitor entry in Year 6.

Case 5 – Current vs New Proposed Guidelines

Original ex-factory Price	\$50,000	
	<i>Current Guidelines</i>	<i>Proposed Guidelines</i>
Price Ceiling	\$48K (assume top of TCC < MIPC)	Ex-factory price ceiling (MLP): \$43K Rebated price ceiling (MRP): (frozen at year 3): \$25K
Tests used to set the Ceiling	Higher of top of TCC and MIPC (substantial improvement)	MLP: MIPC MRP: 50% adjustment to PV price
Ceiling percent reduction from original price	4%	MLP: 14% MRP: 50%
Compliance assessment made against	ATP (rebated price including free goods, but not PLAs)	MLP: ex-factory price MRP: ATP where rebates include PLAs

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Case 6 – Rare disease drug

- Rare disease drug with one indication
- Limited clinical significance (moderate improvement over placebo) but offers hope for the first time for a severe condition with high burden of illness and high unmet need.
- Small treatment population: 1,000 Canadians diagnosed with the condition, 2% increase per year.
 - One in every 4,000 children born are affected by the condition.
- Annual treatment cost: \$300,000
- Potential annual revenues based on the total treatment population: \$300M
- Category 1 based on projected market size, annual treatment cost above GDP/capita

Case 6 – Application of the Proposed Guidelines

Factor	Intro Period	End of Year 1	End of Year 2	End of Year 3*	End of Year 4	End of Year 5	End of Year 6
MLP (set by MIPC)	\$240K	\$240K	\$240K	\$240K	\$240K	\$240K	\$240K
PV Threshold Price**	N/A	\$60K	N/A	N/A	N/A	N/A	N/A
Revenue at PV Price	N/A	\$3.0M	\$6.1M	\$9.4M	\$12.7M	\$19.9M	\$23.6M
Market Size Adjustment***	N/A	2xPV	2xPV	2xPV	2xPV	2xPV	2xPV
MRP	N/A	\$120K	\$120K	\$120K	\$120K	\$120K	\$120K
Total revenue at MRP	N/A	\$6.0M	\$12.2M	\$18.7M	\$25.4M	\$39.8M	\$47.2M

*MLP/MRP frozen.

**CADTH estimated ICER is \$300K-700K, depending on population and severity. Assume 80% price reduction required to meet PMPRB PV threshold of \$60K/QALY.

***Positive market size adjustment owing to small market size – lower of MIPC, 2xPV Threshold price.

Case 6 – Current vs New Proposed Guidelines

Original ex-factory Price	\$300,000	
	<i>Current Guidelines</i>	<i>Proposed Guidelines</i>
Price Ceiling	\$240K	Ex-factory price ceiling (MLP): \$240K Rebated price ceiling (MRP): (frozen at year 3): \$120
Tests used to set the Ceiling	Midpoint of top of TCC and MIPC (moderate improvement, no comparators)	MLP: MIPC MRP: 2xPV price
Ceiling percent reduction from original price	20%	MLP: 20% MRP: 60%
Compliance assessment made against	ATP (rebated price including free goods, but not PLAs)	MLP: ex-factory price MRP: ATP where rebates include PLAs

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Appendix 7: Disclaimers

Appendix 7.1: Disclaimer from the PMPRB

The PMPRB provided the chair with the following disclaimer:

“The views expressed herein are those of the author and of the parties to whom certain views are attributed and should not be understood to constitute or reflect the views of the PMPRB or the Government of Canada unless specifically stated.”

Appendix 7.2: Disclaimer from Innovative Medicines Canada

Frédéric Lavoie provided the chair with the following disclaimer on behalf of Innovative Medicines Canada (IMC):

“IMC understands that the PMPRB intends to take steps to modernize its Guidelines within the framework of the proposed amendments to the Regulations. While IMC is committed to constructive engagement with the PMPRB on Modernization of Price Review Process Guidelines, our participation on the Steering Committee and the Working Group should not be interpreted as supporting the proposed amendments to the Regulations. IMC continues to have serious policy and process concerns about the proposed amendments and reserves its right to oppose the proposed amendments and the work of the Steering Committee and Working Group to the extent it is intended to implement or reflect the proposed amendments. IMC also has many concerns with the June 25, 2018 Guideline Proposals and will provide more detailed commentary once we have had an opportunity to fully assess their potential impacts on patentees. With respect to the Working Group’s governance, IMC intends to participate constructively but is concerned that minority and/or dissenting opinions should be fully and accurately placed on the record throughout the process including the draft and final report from the working group and the publication, following a request from one or more Working Group members.”

Appendix 8: External Review of Draft Report

The following is an external review of the draft report conducted by Dr Mark Sculpher from the Centre for Health Economics at the University of York.

This review was emailed to the chair on 4 March 2019.

General comments

Overall, the report reads well, and the guidance and advice offered to the PMPRB seems appropriate and well balanced.

Chair's response: *I would like to thank Dr Sculpher for reviewing the draft report and providing a number of thoughtful comments. I have responded to each of these below.*

I have struggled to understand the role of PMPRB in relation to the CDR and provincial HTA arrangements. Presumably these different levels of policy review of drug prices will work synergistically and coherently. It seems to me that the most obvious version of such arrangements would be for PMPRB to set a ceiling price which CDR/provincial HTA to take as a maximum which may not be considered cost-effective from the perspective of a given province, indication or patient sub-group. In other words, PMPRB's ceiling price becomes a starting point for further evidence review, analysis and price negotiation that may very well bring prices down further. As such, some of the challenges considered in the report may well simplify (see below). Although this is not the remit of the report, there does seem to be a need to consider how PMPRB will work with CDR and provincial HTA, avoiding duplication and contradiction.

Chair's response: *There are many possible approaches for setting a single ceiling price across multiple provinces, indications and/or patient subgroups. The Working Group recognized that the choice of which approach to adopt is a matter for policy makers. As a result, the Working Group did not advocate for any specific approach. Instead, we considered the technical implications of several possible approaches, in order to support policy makers in coming to an informed decision regarding which approach to adopt.*

Dr Sculpher proposes a specific arrangement under which the PMPRB first sets a ceiling price informed by the maximum price at which a medicine is 'just' cost-effective within a

single province, indication or patient subgroup, and then the price is negotiated down further using other mechanisms at the provincial level. The Working Group discussed some of the technical implications of such an arrangement. It was noted that provinces with lower supply-side thresholds might not have the negotiating power to bargain down the price to a level at which consumer surplus is positive for that province. As a result, such an approach might result in diminished population health in these provinces, which might in turn result in diminished population health across Canada as a whole.

The report covers the key areas of evidence and analysis that I would have expected given the policy context, with three exceptions. The first is the importance of patient-level heterogeneity. There is considerable discussion about pricing by indication, but the same issues exist in relation to patient sub-groups within an indication. There is a trade-off between the product's ceiling price and the number of sub-groups for which it would be cost-effective. This is particularly obvious for products where cost-effectiveness is a function of the underlying risk of a clinical event (e.g. heart disease, osteoporosis etc), but it also applies to a large proportion of pharmaceuticals in other disease areas. I will come back to this below.

Chair's response: *I agree with Dr Sculpher that patient heterogeneity within an indication is an important consideration. As a result of this heterogeneity, there might be specific patient subgroups within an indication that are more cost-effective to treat than others.*

In principle, the implications for consumer and producer surplus of setting a single ceiling price across patient subgroups within an indication are similar to those associated with pricing across multiple indications (as considered in the Conceptual Framework). Among many possible approaches, the ceiling price might be informed by the price at which:

- 1. The most cost-effective patient subgroup is 'just' cost-effective to treat (resulting in negative overall consumer surplus within the indication in question);*
- 2. The least cost-effective patient subgroup is 'just' cost-effective to treat (resulting in positive overall consumer surplus within the indication in question);*
- 3. The 'average' patient within the subgroup is 'just' cost-effective to treat (resulting in zero overall consumer surplus within the indication in question).*

The second area where I would have expected more to be said relates to why there should be interest in producer surplus. A good deal of the report (most notably the first appendix on the conceptual framework) focuses on the balance between producer and consumer surplus, but the interest in the former is surely only because of its anticipated link with enhanced consumer

surplus in the future. The challenge is that there is little evidence on how much producer surplus is necessary to generate future consumer surplus, particularly in an individual and relatively small market. So much of what is in the report hinges on how much producer surplus (or probability of that surplus) should the system 'give away' now to incentivize research and development to generate future consumer surplus, but there is no discussion about how this might be determined given existing evidence.

Chair's response: *It is for policy makers to decide upon the appropriate balance between consumer and producer surplus. The Working Group therefore did not take a position on whether greater producer surplus is inherently desirable or, as Dr Sculpher suggests, is desirable only if it results in greater consumer surplus in the future. Instead, the Working Group considered some of the potential implications for producer surplus associated with various possible approaches for informing a ceiling price.*

A related issue here is that the report often talks about consumer and producer surplus during a product's patent period as if it exists in perpetuity. For example, on page 26, in looking at the implications of a different supply-side thresholds across provinces. The implications of a patent ending for prices and consumer and producer surpluses under different policies seems relevant to consider.

Chair's response: *The Working Group discussed the potential for prices to fall following patent expiry, with implications for the allocation of consumer and producer surplus over the long term. However, in a July 2018 document prepared for the Working Group (Appendix 5.4), the PMPRB clarified that the purpose of the PMPRB is to ensure that patentees "do not charge excessive prices during the statutory monopoly period". As a result, the Working Group focused only on the price during the statutory monopoly period.*

The final element of evidence and analysis on which I would have expected to see more relates to uncertainty. There is good coverage of the underlying challenges of uncertainty in the evidence and modelling and its implications for decision uncertainty, but I was surprised there was not more on policy responses to this and implications for ceiling prices. I am thinking here about frameworks that consider the value of additional evidence, whether evidence can be generated alongside reimbursement, the implications for irreversible costs and the importance of a product's price and its flexibility (e.g. Claxton *et al*). A reasonable response to this critique is that PMPRB only have one 'policy decision' in the domain of value and resources, namely setting a ceiling price. But more could perhaps have been said about what this means for

provincial HTA bodies which could, in principle, have other policy levers at their disposal such as funding only in research, funding alongside research and further price reductions.

Chair's response: *I agree with Dr Sculpher that uncertainty has important implications for provincial decision makers, who may have a variety of policy levers at their disposal. However, the purpose of the Working Group was to provide specific technical recommendations to the Steering Committee regarding how the PMPRB might inform a ceiling price for a new medicine, so these implications were considered out of scope.*

Specific comments

Page 22: The implication here is that supply side thresholds are only relevant to systems with a constrained budget. This is not the case: all systems have many other opportunities to enhance patient benefits, so incur opportunity costs when they make investment decisions (see Sculpher et al).

Chair's response: *I agree with Dr Sculpher. The text on p.22 has been revised to remove reference to a "constrained budget".*

Page 28: It may be worth emphasising that any equity weights used as part of analysis supporting pricing and reimbursement decisions should also be applied to the empirical supply-side threshold.

Chair's response: *I agree with Dr Sculpher that equity weights, if adopted, should also be applied to patients who bear the opportunity cost. Approaches for doing this include weighting the QALYs forgone directly, or adjusting the cost-effectiveness threshold. However, the latter approach has limitations that do not apply to direct QALY weighting.¹⁹ The existing text notes that "there is also an ongoing and unresolved debate regarding whether weights should be applied directly to QALYs or to the cost-effectiveness threshold". I have not made any revisions to the text in response to this comment.*

Page 29: I was unclear how the PMPRB process would give information about the location of the demand curve if its focus is the maximum price a product should command in Canada. There would presumably also need to be information about the relationship between lower prices that might emerge from the provincial HTA process and volumes.

Chair's response: *The Working Group recommended that “any estimate of the supply-side threshold adopted by the PMPRB for the purposes of informing a price ceiling be clearly specified, so as to reduce uncertainty for stakeholders” (Recommendation 2.7).*

This would provide information to stakeholders on the location of the demand curve, given the incremental cost and effectiveness of the medicine in question.

Regarding the supply curve for new medicines, are there examples of any health system being able to estimate this credibly? I am not aware of any and, if that's the case, it would be helpful to reflect on its implications for the PMPRB process.

Chair's response: *Difficulties associated with estimating supply curves, and some potential implications for the PMPRB, are noted throughout the Conceptual Framework. These implications include the potential that ceiling prices might be lowered to the extent that new medicines are not launched, potentially resulting in a loss in economic surplus and negating any positive consumer surplus that might otherwise have arisen.*

Page 32: There may be a case to mention in Section 2.3.9 the distinction between a policy threshold (i.e. the cost per QALYs (or its range) which generally leads to a positive funding/pricing decision) and an empirical estimate of the supply-side threshold. These are often confused in my experience and the examples of 'thresholds' quoted in this page are instances of the former rather than the latter.

Chair's response: *I agree with Dr Sculpher. The text on p.32 has been revised to change all references to a non-supply-side “threshold” to “policy threshold”.*

Page 34-35: This section could be repeated in the context of patient sub-groups by indication, but I saw no mention of this.

Chair's response: *I agree with Dr Sculpher that individual level heterogeneity is an important consideration. However, since the Working Group did not explicitly consider approaches for setting a ceiling price across heterogeneous patient subgroups within a single indication, I have not modified the text in this section.*

I return to the point mentioned under 'general comments', that if PMPRB is defining a maximum price, then surely option 2 is appropriate. This would allow provinces to make decisions and undertake negotiations that involve bringing the price down so that other indications are also cost-effective.

This point could be generalised to cover deliberations regarding the choice of supply-side threshold (given variation across jurisdictions), patient sub-groups and reflecting uncertainty. That is, the PMPRB defines a maximum price, and the provinces may come down from that to reflect lower supply-side thresholds, agreement to include more sub-groups as well as indications, and the implications of uncertainty.

Chair's response: *As noted earlier, the choice of which approach to adopt is ultimately a matter for policy makers. As a result, the Working Group did not advocate for any specific approach but instead explored the technical implications of several possible approaches.*

Page 38: I wonder whether invoking the concept of 'risk neutrality' and 'risk aversion' is helpful here. The underlying normative starting point for the report is a set of objectives relating to population health (perhaps augmented with equity considerations), rather than an unspecified utility function. What role is there, therefore, is considering risk preferences?

Chair's response: *As noted in the Conceptual Framework, uncertainty raises the potential that the actual impact of a new medicine on population health at a given ceiling price is negative, even if the expected impact on population health is zero.*

If the PMPRB is 'risk neutral' then this is offset by the possibility that the actual impact on population health is positive, such that no adjustment is needed to the ceiling price.

However, if the PMPRB is adverse to the risk that the actual impact on population health is negative, then it may wish to lower the ceiling price. This would increase the expected impact on population health and reduce the risk that the actual impact is negative.

The latter position represents a departure from the default assumption of risk neutrality. However, the implied objective is still “related to population health (perhaps augmented with equity considerations)”. Specifically, the implied objective is related not only to the expected population health but also the distribution of uncertainty around the expected population health, in both cases potentially augmented with equity considerations.

The Working Group was unaware of the PMPRB’s precise risk attitude, and did not attempt to specify a “utility function” to account for any potential risk aversion. Rather, the Working Group acknowledged that the PMPRB might adopt an approach to risk that departs from the default assumption of risk neutrality, and noted that this would have implications for the specification of a ceiling price.

Page 45: The term ‘societal perspective’ is used quite loosely here. It may be helpful to be more specific about what this means and how it aligns with a general normative starting point of objectives relating to population health and opportunity costs relating to health care resources.

Chair’s response: *On the previous page, reference is made to the CADTH guidelines which explicitly specify the differences between a ‘public health care system’ and ‘societal perspective’ (see “Differences between perspectives” on p.44).*

I agree with Dr Sculpher that the use of a societal perspective raises important questions regarding the normative position with respect to population health and opportunity costs. As noted in the text, one Working Group member argued that “adopting a societal perspective implies that policy makers are willing to trade health benefits for other societal benefits, which may not be the case”. Other members noted that a societal perspective raises “ethical concerns, including the potential for productivity to be valued less for those with lower earning power”, which may not align with the preferred normative position. I have not made any modifications to the text in this section in response to this comment.

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