Submission to Patented Medicine Prices Review Board (PMPRB) regarding proposed amendments to the definition of Gap medicines, references to comparator countries and the international price tests for Grandfathered medicines and their line extensions

August 31, 2021

On behalf of the signatories to this submission, we present the analysis and Recommendations for the proposed amendments to the definition of Gap medicines, references to comparator countries and the international price tests for Grandfathered medicines and their line extensions, proposed by PMPRB on July 15, 2021.

First, we would like to reiterate our support for the Recommendations previously provided in submissions to PMPRB and Health Canada regarding the proposed regulatory and Guideline changes to date.

See Appendices to this document for previous submissions:

Submission	Date	Appendices
Guideline Monitoring and Evaluation Plan 2021	June 21, 2021	Appendix A
PMPRB Draft Guidelines Consultation 2020	August 4, 2020	Appendix B
November 2019 Draft Guidelines	February 14, 2020	Appendix C
Protecting Canadians from Excessive Drug Prices: Consulting on Proposed Amendments to the Patented Medicines Regulations – 2017	June 28, 2017	Appendix D

As regards the present proposed Guideline changes, we provide the following submission.

1. The Proposed International Price Tests for Grandfathered Medicines and their Line Extensions

The introduction of yet another set of substantive amendments at this late date in the process by PMPRB, with no advanced discussion, underscores the ongoing breach of the rules of natural justice and fairness required by a quasi-judicial body, described in detail in our Submission to the Guideline Monitoring and Evaluation Plan (GMEP)[1] consultation (see **Appendix A**). When asked for a consultation to discuss these latest proposed changes including an explanation for the reasons for them, all that was provided was a page of Frequently Asked Questions that added no meaningful new information in developing a submission.

PMPRB is required to provide a reasonable explanation for its decisions. In this regard, we would refer to the recent *Alexion Pharmaceuticals Inc. v. Canada (Attorney General)* regarding a decision by PMPRB. In para 25, the Court concluded "a reviewing court must ultimately be satisfied that the [administrator's] reasoning 'adds up'."[2]

The Court indicated that the requirement in some cases of a reasoned explanation is higher than in others:

> "In some cases, however, the requirement of a reasoned explanation is higher:
>
> Where the impact of a decision on an individual's rights and interests is severe, the reasons provided to that individual must reflect the stakes. The principle of responsive justification means that if a decision has particularly harsh consequences for the affected individual, the decision maker must explain why its decision best reflects the legislature's intention."

The Court, citing *Vavilov,* stated that:

> "A reason explanation has two related components:
>
> - *Adequacy*. The reviewing court must be able to discern an "internally coherent and rational chain of analysis" that the "reviewing court must be able to trace" and must be able to understand. Here, an administrator falls short when there is a "fundamental gap" in reasoning, a "fail[ure] to reveal a rational chain of analysis" or it is "[im]possible to understand the decision maker's reasoning on a critical point" such that there isn't really any reasoning at all: *Vavilov* at paras. 103-104.
>
> - *Logic, coherence and rationality*. The reasoning given must be "rational and logical" without "fatal flaws in its overarching logic": *Vavilov* at para. 102. Here, the reasoning given by an administrator falls short when it "fail[s] to reveal a rational chain of analysis", has a "flawed basis", "is based on an unreasonable chain of analysis" or "an irrational chain of analysis", or contains "clear logical fallacies, such as circular reasoning, false dilemmas, unfounded generalizations or an absurd premise": *Vavilov* at paras. 96 and 103-104."

Patient groups are not in a position to evaluate the severity of the impact of this decision. There is no doubt, however, that changing the price for some Grandfathered Medicines from the Highest International Price (HIP) to the Median International Price (MIP) of the Schedule Countries will certainly have implications on pharmaceutical company prices, implications that will undoubtedly vary from product to product and across companies.

Whether this change will be detrimental to patients or not cannot be measured by patient groups, as we have no information about company pricing decisions, nor should we be expected to comment on the substantive implications of this. It is, however, another example of the PMPRB exceeding its jurisdiction as a quasi-judicial body in the process it uses to make its decisions.

We do submit, however, that PMPRB has provided neither adequacy, nor logic, coherence and rationality as required by the Court. In cases where these criteria are not met, PMPRB is required to redetermine the matter.

Our recommendation therefore aligns with the Court's finding in para 33 of *Alexion Pharmaceuticals Inc. v. Canada (Attorney General)*[2]*:*

> "In the end, for the reasons that follow, this matter should be sent back to the Board for redetermination. In redetermining this matter, it will be for the Board—in an open-minded, non-tendentious way—to examine the evidence, interpret the legislation, fairly apply the legislation to the evidence and ensure that a reasoned explanation for its outcome can be discerned."

Recommendation 1

Health Canada should require the PMPRB to redetermine this proposed Guideline change in a manner that is open-minded, non-tendentious, that examines the evidence, interprets the legislation, fairly applies the legislation to the evidence, and ensures that a reasoned explanation for its outcome can be discerned.

2. Proposed Transition Period for Compliance

The Regulations were originally planned to take effect on July 1, 2021. The PMPRB consulted with stakeholders on the transition period that would be reasonable for them to come into compliance with the Regulations and decided to permit a 12-month compliance period.

Since that time, the government has extended the coming into force of the Regulations to January 1, 2022, however, the PMPRB has not extended the compliance period to align with the earlier commitment for a 12-month compliance period.

Patient groups are obviously not in a position to comment on the potential implications of this decision. It does, however, provide another example of the breach of the rules of process by PMPRB by unilaterally rescinding a previous agreement reached through stakeholder consultations.

Recommendation 2

Health Canada must instruct PMPRB to withdraw this compliance related Guideline and meet the commitment previously made for a 12-month compliance period from the coming-into-force date of the Regulations, *i.e.* January 1, 2023 operative date for assessing compliance.

3. General Recommendation Regarding PMPRB Processes to Date

Perhaps most egregious is the fact that the complete set of changes to the Guidelines and the creation of the Guideline Monitoring and Evaluation Plan (GMEP) were not presented at one time in order that they could be considered as a whole with all the implications of the changes for patients, including those for discreet patient groups, so that a meaningful and complete submission could be made on behalf of patients.

It is also entirely inappropriate for PMPRB to change Guideline proposals on which they have previously consulted.

The law with regard to the conduct by quasi-judicial bodies, the Health Canada and Public Health Agency of Canada Guidelines on Public Engagement[3] and the *Alexion Pharmaceuticals Inc. v. Canada (Attorney General)*[2] decision all highlight the lack of due process since the outset of the PMPRB consultations on the Regulations and Guidelines.

Recommendation 3

Health Canada should exercise its responsibility to re-evaluate the PMPRB's policies, processes and plans to ensure PMPRB compliance with its legal and government policy obligations in the area of drug pricing, as set out above, since the outset of this process which began in 2016. A public report back should be made available by Health Canada on its findings.

In the interim, this requires a hold on all proposed PMPRB Guideline changes.

4. Closing Comments

Patient groups have been engaging with the Health Canada and the PMPRB since the outset of the announcement of changes to the drug pricing regulatory regime at the federal level.

We have continued to advocate for changes that will ensure that excessive pricing rules are maintained while ensuring that the impact of such changes will not inhibit entry of much needed innovative medicines into the Canadian market, nor will delay such entry. We have also continued to express our concern about the implications on clinical trial launches in Canada. While the federal government has recently launched a biomanufacturing and life sciences strategy for Canada on June 28, 2021, the Health Canada drug proposed regulatory changes for drug pricing appear to be inconsistent with the goals of that strategy.

It is profoundly disappointing to patients and their representatives that after all of the engagement initiatives in which we have participated constructively and in good faith, we continue to be faced with a quasi-judicial body that is failing Canadians by continuing to conduct itself in a manner that is biased, partial and lacking an objective analysis of the evidence provided to it.

5. Signatories

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6. References

1. Patented Medicines Prices Review Board (PMPRB). *PMPRB Guideline Monitoring & Evaluation Plan 2021*.; 2021. https://www.canada.ca/content/dam/pmprb-cepmb/documents/consultations/gmep/PMPRB-2021-GMEP-en.pdf.
2. Alexion Pharmaceuticals Inc v Canada (Attorney General), [2021] FCJ No 812, 2021 FCA 157
3. Health Canada, Public Health Agency of Canada. *Guidelines on Public Engagement*.; 2019. doi:H14-153/2019E-PDF

Appendix A

Guideline Monitoring and Evaluation Plan 2021 Submission

Submission to Patented Medicine Prices Review Board (PMPRB) regarding Guideline Monitoring & Evaluation Plan (GMEP) 2021

June 21, 2021

On behalf of the signatories to this submission, we present the analysis and Recommendation for the Guideline Monitoring & Evaluation Plan (GMEP) 2021 proposed by PMPRB in June 2021.

1. Foundational Principles Regulating PMPRB

1.1. Legal Obligations of the PMPRB

The PMPRB is a quasi-judicial agency of the federal government created under *the Patent Act.*[1] It reports in through Health Canada for purposes of the drug pricing Regulations while other parts of the *Act* report in through the Minister of Innovation, Science and Economic Development. It is responsible to determine whether the price being proposed for the sale of a drug or other treatment in Canada is excessive. If the price is deemed to be excessive based on the criteria set out in the Regulations to the *Patent Act*, the manufacturer must lower the price to meet these criteria or will not be permitted to sell the product in Canada.

Quasi-judicial bodies including Agencies, Boards, and Tribunals, make decisions on behalf of the government, when it is impractical or inappropriate for the government to do so itself. They must behave impartially in their decision-making process.[2]

Quasi-judicial bodies are under a duty to act in accordance with the rules of natural justice, giving persons specially affected by the decision a reasonable opportunity of presenting their case, listening fairly to both sides and reaching a decision untainted by bias.[3] They also have the right to engage specific expertise to assist in providing needed advice and input.[2]

The rules of natural justice apply to all decision makers and those advising them, *e.g.,* the Board of Directors, the staff of PMPRB and any advisors on whom they rely.

Since these bodies are created to move tasks, in whole or in part, out of the traditional parliamentary and Cabinet processes, the agency itself should opt for public involvement in the decision-making process.[4]

1.2. Government Policy Obligations of the PMPRB

In conducting its role as the decision maker regarding excessive drug pricing in Canada, the PMPRB reports in through Health Canada. Public engagement activities by the PMPRB should therefore align with the principles outlined in the Health Canada (HC) and the Public Health Agency of Canada (PHAC) Guidelines on Public Engagement, published November 2019.[5]

These Guidelines recognize the importance of public engagement as an important part of the democratic process and allows Health Canada and the Public Health Agency of Canada to fulfill key responsibilities, including the following:

- "Foster information exchange and knowledge sharing to improve the understanding of health issues and build relationships among interested and affected parties"[5]
- "Facilitate discussions between HC and PHAC and individuals, groups and organizations, external to the Government of Canada, to provide opportunities to shape government policies, programs, services and regulatory initiatives" [5]

- "Consider the feedback and perspectives of individuals and groups in the development or assessment of government policies, programs, services and regulatory initiatives in order to inform decisions"[5]
- "Enable informed decision-making that ultimately fulfills the mandates of HC and PHAC and improves the health and safety of Canadians"[5]

The Guidelines define public engagement as planned two-way discussions with individuals, organizations, or groups, external to the Government of Canada, designed to gather input, clarify information and foster understanding among those interested and affected by an issue, decision or action and to better inform HC and PHAC's decision-making. Public engagement activities should include key stakeholders directly impacted, namely patients and patient groups, Indigenous Peoples and groups, caregivers, people with disabilities and health care providers.[5]

The Guidelines are based on the following fundamental principles of meaningful public engagement:

- **Openness and Inclusiveness**
    - Designed and promoted to provide opportunity to all interested participants to provide input.
    - Engagement activities available through variety of formats to remove barriers to participation.
- **Timeliness and Transparency**
    - Purpose, scope and objectives are clearly communicated and planned.
    - Provide sufficient time for interested stakeholders to participate.
- **Relevance and Responsiveness**
    - Engagement activities are participant-focussed.
    - Materials designed to facilitate engagement activities and to meet engagement objectives.

It is important to note that "public engagement" has a broader meaning than "consultation," reflecting a wider variety of interactions and outcomes ranging from informing the public to engaging in dialogue. It can consist of one or more activities depending on the complexity of the issue, the potential impact, and the diversity of impacted stakeholders. The greater the potential impact on affected and interested participants, the higher the level of engagement and reporting back should be. Additionally, highly technical issues of narrow relevance require a focused and detailed public engagement approach at the dialogue level, while issues potentially impacting a broad range of stakeholders with diverging points of interest requires larger engagement activities to inform, listen and discuss.[5] Examples of public engagement approaches are presented in **Table 1**.

Table 1. Common Approaches to Public Engagement. Adapted from Health Canada and the Public Health Agency of Canada Guidelines for Public Engagement, 2019.[5]

Approach	Description	Benefits	Challenges
In-person discussion sessions	• Participants attend a group session involving presentations and/or discussions.	• Opportunity for open dialogue among participants and decision-makers. • Effective for gathering input on preliminary options or ideas.	• More costly and time-consuming than alternatives. • Subject to availability of participants at a specific time and location
Online interactive platform	• Participants join an online discussion forum to discuss issues and share their views with others.	• Opportunity to gain perspectives from participants from regional or remote areas at their convenience. • Flexible approach which can be designed and adapted based on objectives and adjusted throughout the engagement.	• Time consuming to design, implement, moderate, and monitor. • Requires planning and resources to summarize and analyze feedback.
Online questionnaire	• Opportunity to participate is posted online or emailed to targeted participants with a link to the questionnaire. • Participants complete the questionnaire and submit it directly online.	• Opportunity to gain perspectives from participants from regional or remote areas at their convenience. • Flexible approach which can be designed and adapted based on objectives.	• Time consuming to design, deliver and monitor. • Participants cannot benefit from hearing the different perspectives of others. • Requires planning and resources to summarize and analyze feedback collected.
Request for feedback	• A draft document or proposal is posted online or emailed to target audience and participants are asked to provide general feedback by email.	• Cost-effective way to receive detailed, meaningful feedback on drafts or proposals. • Specific information can be obtained in a controlled manner.	• Participants cannot benefit from hearing the different perspectives of others. • Requires planning and resources to summarize and analyze feedback

When an appropriate public engagement activity is chosen and designed, the initiative can be launched, and the process and outcomes of the engagement initiative should be evaluated to determine its success and allow for continuous improvement.

2. The Guideline Monitoring & Evaluation Plan (GMEP)

2.1. Implications of the Nature and Scope of GMEP

The PMPRB proposes to do an analysis in 4 key areas, the first 3 of which are drug pricing, access to treatments and the pharmaceutical ecosystem.

These are extremely complex health economic areas. They also hold the highest significance for people living in Canada. There is no greater potential impact on affected and interested participants than government decisions impacting access to live saving and quality of life enhancing medications. As such, the highest level of public engagement is warranted. In addition, technical advisors must display a history of unbiased, evidence-based analysis in this area.

The PMPRB has recognized this to some extent by indicating that it will identify relevant indicators to monitor **in consultation with its stakeholders**.

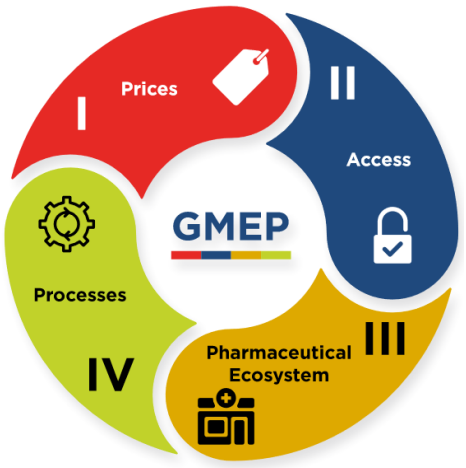

Figure 1. Diagram of the 4 key areas of the PMPRB Guideline Monitoring & Evaluation Plan. Copied from PMPRB GMEP 2021 consultation document.[1]

The indicators that the PMPRB proposes to monitor and assess in the Prices, Access and Pharmaceutical Ecosystem areas require interpretation in the context of the health policy environment in Canada and internationally. The PMPRB does not have such expertise in-house. In fact, much of this information is only available through specific stakeholders who can help with the collection, analysis and interpretation of key indicators.

The causal links between PMPRB Guidelines and Prices, Access and Pharmaceutical Ecosystem indicators, including clinical trial intensity, availability of new medicines, system coordination, drug spending, research and development and economic footprint, are of immense complexity. Therefore, the monitoring and evaluation committee must include expertise from diverse stakeholder groups that can provide context on the forces that are driving changes in those indicators based on an understanding of the entire healthcare environment and its dynamic nature.

We submit that by the quasi-judicial nature of the PMPRB, the duty to hold the highest level of public engagement in its proceedings, and its unilateral decision to select technical advisors without any stakeholder consultation clearly demonstrate the need for a GMEP that is transparent, evidence-based and impartial, and with multistakeholder membership.

While the technical advisors selected may well have expertise in this area, the public pronouncements of some members violate the duty of impartiality required by the PMPRB.* Thus, a full review of this decision must be undertaken and a transparent selection process, including opportunity for stakeholder engagement must be implemented. Patient group stakeholders and no doubt other stakeholders as well will be more than willing to offer suggestions about experts that have a history of unbiased technical expertise for your consideration.

Recommendation

Health Canada should exercise its responsibility to evaluate the PMPRB's policies, processes and plans to ensure PMPRB compliance with its legal and government policy obligations in the area of drug pricing, as set out above. A public report back should be made available by Health Canada on its findings.

In alignment with the principle of continuous improvement, Health Canada should direct PMPRB to make appropriate modifications based on the findings from the evaluation.

This process should be undertaken by Health Canada whenever the PMPRB is making changes to its Guidelines and other planning processes.

3. Conclusions

Based on the analysis of the legal and government policy obligations of the PMPRB in relation to public engagement and the conduct of its mandate, the GMEP must be entirely re-designed in accordance with recommendation above.

4. Signatories

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*It is clear from the public stances expressed by a number of the technical advisors that they have inherent biases with regard to particular stakeholder groups, namely patients, patient representatives and pharmaceutical industry.

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Antonella Scali, Executive Director, Canadian Psoriasis Network (CPN)

5. References

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Appendix B

PMPRB Draft Guidelines Consultation 2020 Submission

CONECTed
Collective Oncology Network for Exchange, Cancer Care Innovation, Treatment Access and Education

RCONECTé
Réseau collectif d'oncologie pour échange, innovation en soin du cancer, accès aux traitements et éducation

Patented Medicine Prices Review Board
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Standard Life Centre
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Ottawa, Ontario
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August 4, 2020

re: Oncology Patient Group (CONECTed) PMPRB 2020 Guidelines Input Submission

Thank you for the opportunity to provide feedback on the draft Guidelines published on June 19, 2020.

We, the signatories to this submission, will describe the background to set the context that underpins our deliberations in which we considered the revised draft Guidelines. We will then provide an updated analysis of the case studies that we had provided in our last submission on February 15th 2020 using the draft Guidelines of June 19th 2020 for your consideration (Appendix A), and will follow with recommendations to remedy the concerns we still find with the approach PMPRB is proposing to addressing the entry level price of patented drugs in Canada.

Basis for our position

As patients and patient groups, we recognize the challenges of a dual federal/provincial jurisdiction that underlines the healthcare system for people across Canada.

We are also aware that there are inequities in coverage for medications across the country due to several factors. Public systems are the responsibility of provinces and territories and of course each has its own economic engine, priorities, demographics and other factors that drive decisions about how much to spend, what to fund and what funding models to implement. In addition, employers, unions, and individuals who can afford them have private plans that provide additional access.

Patients accept that this is the construct we have. We understand that public plans drugs have to make decisions about drugs they fund although we trust that they will use instruments that will help make fair, objective and evidence-based choices. We all want a sustainable system; we want the prices of drugs to permit sustainability. This is no doubt the appeal of a universal single payer pharmacare plan. We are not against it, but it needs to fairly ensure Canadians have access to the care they deserve.

Patient groups, such as the ones we represent, continue to support health technology assessment agencies, CADTH and INESSS, and also pCPA. They each play a key role for the constituents they serve and operate on a value system to provide better health to Canadians.

In the case of PMPRB, we continue to believe its mandate can be modernised at this time by reassessing the current basket of reference countries proposed in the current review. The other agencies listed above have the role of determining clinical and economic value and to negotiate confidential reimbursement prices to reach a mutually agreed drug price with the drug manufacturers and the provinces.

It is important to revisit the history of cancer management in Canada, as it serves as a guiding principle to our position:

- In 2007 the House of Commons Standing Committee on Health heard evidence that cancer treatments required their own health technology assessment process to ensure that value is analyzed based on factors relevant to that complex group of diseases. The Committee agreed with these recommendations. The result of those hearings was the creation of pCODR with a four-part deliberative Framework as its HTA process.
- The federal government also created a cancer strategy stewarded by the Canadian Partnership Against Cancer.
- Provinces have cancer agencies to manage cancer generally, including drug reimbursement, separately from other treatments.

The statistics regarding cancer certainly make the case for this specific focus on cancer:

- It is the number 1 cause of death in Canada.[1]
- It is estimated that 1 of 2 people in Canada will be diagnosed with cancer in their lifetime.[2]
- 1 in 4 will die from it, or 821,000 in Canada this year alone.[2]

This is a huge public health issue that requires a discrete policy approach, as the governments have recognized.

In addition, as we know, there is not just one type of cancer, one stage of cancer or one cause of cancer:

- There are cancers that are uncommon and those that are more common.
- There are cancers for which research has found genetic links that inform prevention and treatment and those that have not.
- There are cancers that can be cured.
- There are cancers that can be effectively treated and have been transformed into chronic illnesses with newer, more effective treatments; yet, there are many that continue to be a certain death sentence within months of diagnosis.

Breast cancer: The most common cancer among women, both young and old people alike, is breast cancer. In 2020, an estimated 27,400 women will be diagnosed with breast cancer and 5,100 will die of this disease. Additionally 240 men will also be diagnosed with breast cancer.[3] Among women, between 5 and 10% of breast cancers are thought to be hereditary. The BRCA1 and BRAC2 have been known to be linked with a higher link of breast cancer.[4] More recently, a study in 2017 found 72 new genetic mutations linked to breast cancer and now under study.[5]

Colorectal cancer: Among cancers, Colorectal Cancer is the second leading cause of death in men, and the third leading cause of death in women.[6] About 50% of cases were found to be diagnosed at stages III and IV,[7] and an estimated 9700 will die of this cancer in 2020.[6]

Lung cancer: It is estimated that this year, 29,800 Canadians will be diagnosed with lung cancer, and 21,200 will die from it.[8] It is the leading cause of cancer deaths for males and females at 25.2% and 26.1% respectively.[9] Contrary to public opinion, it is not just a disease of those who smoke. Unlike breast cancer, most cases of lung cancer are not related to inherited genetic changes.[10] There are certain "signatures" within the lung cancer cell that determine which oral cancer therapies to use.[11] It has a 19% five year survival rate compared to 93% in prostate cancer, 88% in breast and 65% in colorectal.[7]

Paediatric cancers: Every year, around 880 children under the age of 15 are diagnosed with cancer, and 150 die from it. Cancer is the second most common cause of death for children aged 1-14 in the developed world after accidents.[12] Due to access to new treatments, the five-year survival rate for Canadian children has improved from 71% to over 82%.[13] Without treatment these cancers are fatal.[14] While a significant number of children are cured, they face a life time of significant health care impacts including secondary malignancies caused by the treatments that cured them. Cure rates have also plateaued with no improvements in many paediatric cancers over several decades. Reducing the lifelong impacts of treatments and saving the lives of the 20% of children we continue to fail requires new approaches and new treatments.

Blood cancers: Over 21,000 Canadians are expected to be diagnosed with one of 137 different types of blood cancer this year.[15] Dramatic scientific breakthroughs in the past several years have significantly improved our understanding of these diseases and have opened new treatment opportunities that can improve outcomes for patients.[15] Access to the most effective new treatments is therefore especially critical.

Uncommon cancers: There are also uncommon cancers like Gastrointestinal Stromal Tumours (GIST) with unclear prevalence and incidence levels in Canada,[15] but estimated to be about 500 new cases per year.[16] Genetic testing is recommended to guide treatment decisions for high risk resected and advanced GIST.[17]

In our submission, the PMPRB, as a federal government agency, must recognize that government policy has determined that oncology is a discrete group of diseases for public policy purposes. Oncology patient groups and other stakeholders strongly support this policy as a good health policy that is strongly supported in many other countries.

Until the first Guidelines were issued in late November 2019, patient groups had no defined concrete formula or processes by which to determine whether the planned changes will consider public policy regarding oncology, and therefore whether it will be a good public policy instrument or not.

When the 2019 draft Guidelines were released, in order to ensure an objective evidence based and expert analysis of the Guidelines, we asked an external health economist to assist us understand how those formulas in the proposed guidelines would be applied. Specifically, we asked him to look at six oncology drugs for different types of cancer that have been reviewed by pCODR recently, and to compare the outcomes they received through that process with the outcomes we can predict they would have had under the 2019 Guidelines release with the information available to us. The results of these analyses and recommendations based on them were presented to PMPRB during a meeting on February 13, 2020 and submitted formally on February 14, 2020 as a response to the open consultation.

2020 Guidelines – A new opportunity to get it right

We were pleased that the PMPRB delayed the implementation deadline set for July 1 2020 to allow for more time to analyze and comment on the new guidelines released on June 19 2020, with an implementation date now proposed for January 1 2021. In our view, it demonstrated that it had incorporated comments received by the many stakeholders during the February – March 2020 time frame. We welcomed the recognition of the need for a more nuanced approach to assessing "excessive" pricing in the oncology context and that the QALY thresholds that represented major concerns for us had been expanded in a significant way. There are other issues, however, that have emerged with the new guidelines, which we will cover later in this submission.

We provided the 2020 Guidelines to the health economist with whom we had originally worked and asked him to re-evaluate the impact of these changes on our six case study drugs. At the conclusion to this submission is Appendix A, the analysis from the Health Economist.

Revised Case studies analysis

In the appendix we present the new six case studies analysed by the health economist using the 2020 draft Guidelines.

Our conclusions from the cancer case studies analysis using the new formulas

It remains clear that oncology needs its own approach in any Guidelines, as the federal and provincial governments have recognized in other health policies.

It also remains clear that this approach must be flexible enough to recognize the differences between uncommon and more common cancers, different stages of cancer, genetic factors, paediatrics versus adults, comorbidities, Indigenous populations and social determinants of health, to name a few.

We recognize that PMPRB has taken into account our submissions in this area, and has come some way to responding to the concerns of the oncology community. We appreciate the incorporation of a more stratified approach to Category I drugs. It certainly will alleviate some of the concerns we have had about the previous 2019 Guidelines.

In the new iteration of the health economist's analysis, based on expected revenue, and on the Therapeutic Criteria Level(TCL Designation), the MRP calculation requires a percentage reduction of the submitted price by anywhere from 0% (CADTH Best Case) to near 50% (CADTH Worst Case) based on the Therapeutic Criteria Level (TCL) designation.

It is not the role of patient groups to determine what decisions a pharmaceutical company will make about launching new drugs into Canada based on such reductions. It will probably be a case by case decision based on factors which are specific to the business environment and expectations. Decisions not to launch or to delay launch will directly impact access to needed therapies for oncology patients. The uncertainty remains about the availability of a new therapy still exist. In fact, with the introduction of the 4 Therapeutic Criteria Levels, that are assigned to each new therapy,

the PMPRB is introducing a new complexity that will result in an increased uncertainty. It is difficult to feel confident that the new Guideline formulas make it easier, and provide the certainty required, to ensure drug launches in Canada and the availability of clinical trials of medications badly needed by people across the country.

For example, in cancer, depending on the patient's genetic characteristics, a therapy of a lower TCL might work better than one assigned a higher level, therefore possibly impacting the accessibility of this therapy. Definitions of the TCL are open to significant variation in interpretation and it would be wise to have other expert bodies, such as HTA organisations and/or medical experts and including patients to define the value of a new therapy.

CADTH's deliberative framework for oncology drugs, with four considerations, including clinical benefit, cost effectiveness, patient values and feasibility of adoption, has recognized this nuanced, flexible and pragmatic health technology assessment required for oncology drugs. This is a recognition that there are limitations of using a single outcome measure for economic evaluation, since doing so means that important health consequences are excluded. INESSS also takes into account societal and patient values in its health technology assessment considerations.
Based on our review of the entire revised Guidelines provided on June 19, 2020 we submit the following recommendations that will serve to support the modernisation of the PMPRB:

Recommendation #1 – Further consultation is required

We accept that the new 2020 draft Guidelines are an improvement for cancer drugs in general from the 2019 draft Guidelines. The changes that are proposed are significant and will have important consequences.

It must be recognized, however, that decisions about all aspects of drug pricing and launches in Canada, are exclusively within the purview of each company. The decision about whether required price reductions will be acceptable to each company will undoubtedly involve a number of factors proprietary to each company. Therefore, patient groups cannot draw conclusions as to whether these changes will encourage introduction of a drug, and if it will do so in a timely manner. All we care about is that medications be made available to Canadians.

The Guidelines still create a level of uncertainty that may well discourage industry from bringing certain needed drugs to market and this will be detrimental to the health and well-being of patients. The industry has already drawn this conclusion. **Therefore, we ask that further consultations with industry should be undertaken to clarify areas of uncertainty before adoption**. To support this dialogue, we ask that PMPRB provide case studies like we did across the 4 levels of TCL for Category 1 drugs.

Recommendation #2 – Need for Transparent Algorithm

Create and publish an algorithm for how drugs get sorted into the different TCL levels. This algorithm should allow stakeholders to easily identify in which TCL a drug will fall, in order to calculate the associated price reduction.

Current TCL definitions are open to variation in interpretation which could lead to ambiguous cases where it is unclear whether a drug will be considered, for example, TCL1 or TCL2. This ambiguity is problematic since the ICER threshold differences between TCL1 and TCL2 can lead to substantial differences in PEP estimates, and ultimately, the amount of price reduction the drug will be subject to. Likewise, differences in the Reduction Floor values across the TCLs also leads to significant differences in MRP estimates.

This creates uncertainty for key stakeholders such as patentees, pCPA or payer negotiators, who must make pricing decisions in the medium term that match (or better) prices that will be established following PMPRB review.

This uncertainty at the negotiations level can affect decisions by patentees to launch a drug, either leading them to delay the launch until more information becomes available when PMPRB sorts the drug into one of the four TCL levels, or to cancel the launch altogether. This will potentially reduce timely access to much needed drugs, and result in harm to patients.

In conclusion, establishing a clear and transparent algorithm with the input of relevant experts, or more clearly defining the criteria that can be used by key stakeholders to identify the TCL that the drug will fall into, will help prevent potential delays in access for patients that may occur as a result of looming uncertainty.

Recommendation #3 – Implementation in stages

The PMBRB should consider implementing the Guidelines in a staged approach. First, it should implement using the updated 11 baskets of countries as reference for January 1, 2021. The implementation of the pharmaco-economic, GDP and market size factors to follow at a later date closely aligned with our Recommendation #1. A carefully thought out and interrelated roll out with interim evaluations and course correction measures will result in better consequences for all stakeholders.

Recommendation #4 – Multi-stakeholder evaluation and monitoring committee

The Guidelines be amended to provide a multi-stakeholder Committee responsible and accountable to oversee the monitoring and evaluation process of the PMPRB modernisation Guidelines.

This Committee should be tasked with the creation of a multi-stakeholder Panel of experts to review all drugs that are determined to be “excessive” in entry level price by the criteria set out in the Guidelines. This Panel will take into consideration factors other than MRP, including factors taken into account by CADTH in its deliberative framework.

As well a multi-stakeholder subcommittee including patients and patient representatives chosen by oncology patient groups must be implemented to review Category 1 drugs to provide advice to determine the TCL designation for each drug being evaluated.

Recommendation #5 - Patient Engagement

The PMPRB develop a formal patient engagement programme following the ICER model co-created with patient groups chosen by the oncology patient community. https://icer-review.org/announcements/2020_vaf_update/ See particularly pages 50-54.

Recommendation #6- Maintain non-transparency for the benefit of patients

The Guidelines be amended to provide that PMPRB's public decision will provide information that the analysis has either met the PMPRB threshold and is not excessive or that it has not met the PMPRB threshold or other CADTH analysis and is excessive.

No specific economic data or numbers supporting this decision should be made public by PMPRB. This will ensure that the public Canadian price will not put at risk other markets and particularly the U.S. market such that companies will decline to enter, or delay entry to, the Canadian market for that reason.

Thank you for inviting us to provide our comments on the proposed PMPRB guideline revisions. We look forward to hearing back from you at your earliest convenience.

Respectfully submitted,

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Barry Stein, Colorectal Cancer Canada
David Josephy, GIST Sarcoma Life Raft Group Canada
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APPENDIX A - PMPRB ceiling price proposed Guidelines – June 2020
Oncology Case Studies

Introduction

In June 2020, the PMPRB issued its updated draft Guidelines for determining the ceiling prices of patented pharmaceuticals.

For Category I pharmaceuticals, the draft Guidelines now simply note that the Pharmacoeconomic Price (PEP) will be determined from the re-analysis of the base case provided by Canada's HTABs (being information to be supplied by the patentee). Thus while the equation presented in the 2019 Guidelines has been removed from the document, in essence it remains a reasonable means by which to estimate the PEP (as was made clear during consultation on the 2019 Guidelines, the equation was not meant to be considered definitive but simply a guideline). In addition, the 2020 draft Guidelines amends the ICER thresholds to be used in calculating the PEP which are now dependent on the newly introduced Therapeutic Class Level (TCL) into which the drug falls. Further, to calculate the Maximum Rebated Price (MRP), a second test – the Reduction Floor, its level also dependent on the TCL – is used and the higher of the two prices calculated from the PEP or Reduction Floor becomes the default MRP. Finally, the MRP may be adjusted depending on the market sales with the adjustments also being dependent on the TCL (referred to as the MRP[A]).

The effect of these changes on estimates of the MRP/MRP[A] for six oncology (assumed category I) pharmaceuticals is the subject of this report. Note that the Guidelines provide guidance for estimating ceiling prices for all patented pharmaceuticals. However, in this report we restrict our interest to estimating the effect the proposed Guidelines may have on New Chemical Entities being brought to Canada that, in general, are likely to be classed as category I pharmaceuticals because of the proposed prices and as exemplified by the six drugs considered.

This analysis uses the analysis conducted on the 2019 draft Guidelines for the same six oncology drugs. The information collected from the HTA reports to make the calculations for that analysis is used unaltered to estimate the MRPs likely to result from the new algorithm contained in the 2020 draft Guidelines. In order to see the effect of the new ICER thresholds, the impact of the Reduction Floor and adjustments possible due to market size, estimates are made for all TCLs – thus the potential bias from determining which TCL a drug is likely to fall under is removed in favour of providing a range of results.

The six drugs reviewed in this report are as follows:

- Vencexta (venetoclax) – a drug for treating chronic lymphocytic leukaemia (CLL) among patients who have failed at least one prior therapy (and, therefore, have no further treatment options);
- Opdivo (nivolumab) – for (among many other indications) adjuvant treatment of fully resected melanoma;

- Darzalex (daratumumab) – for treatment (in combination with other medicines) of multiple myeloma in patients who have failed at least one other prior therapy (and, therefore, have few further options);
- Blincyto (blinatumomab) – for treatment of pediatric patients with Philadelphia chromosome-negative relapsed or refractory B precursor acute lymphoblastic leukemia (a small group of patients - 40 a year - who face no alternatives and a very high likelihood of death);
- Unituxiini (dinutuximab) – for use in combination with other drugs for the treatment of pediatric patients with high-risk neutoblastoma who achieve at least a partial response to prior therapy (a group of around 25 to 35 children a year); and
- Tagrisso (Osimertinib) - for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) mutations (a relatively large group of around 2,000 patients annually).

Background

In February 2020, the 2019 PMPRB draft Guidelines were analysed to estimate the likely ceiling price for the six oncology drugs listed above and, as a consequence of these estimates, their likelihood of being launched in the Canadian market had the 2019 draft Guidelines been in place at the time they were launched. The analysis indicated that the ceiling prices for these six drugs could range from no/small price reductions (two drugs) through to price reductions in excess of 75 percent/100 percent (four drugs). These results enabled a relatively uncontroversial (even though subjective) conclusion to be drawn – it was reasonable to conclude that had the 2019 draft Guidelines been in place, four of the six drugs reviewed would have been very unlikely to have been launched in Canada.

These results are summarised in the table below:

Estimated plausible price reductions required under the 2019 draft Guidelines and impact on Launch

	cf. Submitted price	cf. Current price	Launch?
venetoclax	80%	70%	Very unlikely
nivolumab	25%	5%	Likely
daratumumab	80%	70%	Very unlikely
blinatumomab	75%	70%	Very unlikely
dinutuximab	0%	0%	Very likely
osimertinib	91%	88%	Very unlikely

Results of 2020 draft Guidelines

The results of the updated analysis using the category I (based on price) calculation algorithm for each of the six oncology drugs is presented on the following pages. Below is a summary of the results exploring the sensitivity of the estimates to TCL classification and revenue.

Estimated plausible price reductions – (at $25M revenue)

	TCL 1	TCL 4	Launch?
venetoclax	0%	26%	Likely
nivolumab	0%	0%	Likely
daratumumab	0%	26%	Likely
blinatumomab	5%	26%	Likely
dinutuximab	0%	0%	Likely
osimertinib	10%	26%	Likely

Estimated plausible price reductions – (at TCL 2)

	< $12M	$125M	Launch?
venetoclax	0%	33%	Likely
nivolumab	0%	16%	Likely
daratumumab	0%	33%	Likely
blinatumomab	0%	33%	Likely
dinutuximab	0%	16%	Likely
osimertinib	0%	33%	Likely

Venclexta (venetoclax)

Estimation of MRP/MRP[A]

Indication (coverage requested): As monotherapy for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy and who have failed a B-Cell Receptor Inhibitor (BCRi)

Item	CADTH Base Case	CADTH Best Case	CADTH Worst Case
ICER threshold - TCL 1 (a1)		200,000	200,000
ICER threshold - TCL 2, 3 and 4 (a2)		150,000	150,000
Incremental QALYs (b)		3	0
Incremental costs (c)		359,506	69,300
Treatment costs (d)		355,409	62,181
Submitted public price (e) - $/mg		0.68	0.68
PharmacoEconomic Price - PEP if TCL 1 (e*(a1*b+d-c/d) - $/vial		0.98	0.02
PharmacoEconomic Price - PEP if TCL 2, 3, or 4 (e*(a2*b+d-c/d) - $/vial		0.73	- 0.00
MRP as percent reduction of submitted price with floor test			
If TCL 1		0%	20%
If TCL 2		0%	30%
If TCL 3		0%	40%
If TCL 4		0%	50%
MRP as percent reduction of submitted price with market size adjustment			
Where revenue < $12M and TCL 1, 2, 3 or 4		0%	0%
Where revenue $25M and TCL 1		0%	10%
Where revenue $25M and TCL 2		0%	16%
Where revenue $25M and TCL 3		0%	21%
Where revenue $25M and TCL 4		0%	26%
Where revenue $125M and TCL 1		16%	27%
Where revenue $125M and TCL 2		16%	33%
Where revenue $125M and TCL 3		16%	39%
Where revenue $125M and TCL 4		16%	45%

Assumptions:

- Estimation of MRP would be determined from the stated indication.
- Treatment cost is not reported in the CADTH reports so treatment cost is estimated from reported median treatment duration and dosing regimen for the submitted base case and then used as a proportion of the incremental treatment costs reported for the best and worst cases.
- Submitted public price is the Maximum List Price (MLP) as price adjustments from the above calculations are applied to the MLP. (Note that the submitted price may be lower with the implementation of the draft Guidelines but the PEP cannot be calculated from the CADTH reports using an assumed lower price as the published CEA results depend on the submitted price. However, a lower submitted price will mean a lower price reduction is required to produce the same PEP.)

Interpretation of results

- The range in PEP price estimates (from 98c per mg through to 0c per mg) given the lack of a base case re-analysis from CADTH shows how uncertain a price based on the PEP alone may be.

- The Reduction Floor reduces this possible variation substantially resulting in prices ranging from no reduction relative to the submitted price (assumed to be the MLP) to a 50% reduction.
- Given the first $12M of revenue may be earned at the MLP, the market size adjustment also significantly attenuates the possible range of required price reductions from none through to 26% (at revenue of $25M) and 45% (at revenue of $125M).
- The results also indicate that the potential price reduction required is significantly affected the TCL classification of the drug.

Overall, given anecdotal evidence of the price reductions sought by the pCPA, these potential price reductions appear manageable and, thus it appears the MRP calculation algorithms themselves may have been unlikely to affect a launch decision had the 2020 draft Guidelines been in place at the time of the launch of osimertinib.

The degree of variation in price reductions likely as a result of the TCL determination and the level of unknowns surrounding this determination in the short term would, however, likely introduce a significant level of uncertainty that could lead to decisions not to, or delay, launch.

Opdivo (nivolumab)

Estimation of MRP

Indication (coverage requested): as monotherapy, for the adjuvant treatment of adult patients after complete resection of melanoma with regional lymph node involvement, in transit metastases/satellites without metastatic nodes, or distant metastases.

Item	CADTH Base Case	CADTH Best Case	CADTH Worst Case
ICER threshold - TCL 1 (a1)		200,000	200,000
ICER threshold - TCL 2, 3 and 4 (a2)		150,000	150,000
Incremental QALYs (b)		1	1
Incremental costs (c)		87,974	87,191
Treatment costs (d)		96,062	102,856
Submitted public price (e) - $/mg		19.65	19.65
PharmacoEconomic Price - PEP if TCL 1 (e*(a1*b+d-c/d) - $/vial		55.25	38.14
PharmacoEconomic Price - PEP if TCL 2, 3, or 4 (e*(a2*b+d-c/d) - $/vial		41.85	29.36
MRP as percent reduction of submitted price with floor test			
If TCL 1		0%	0%
If TCL 2		0%	0%
If TCL 3		0%	0%
If TCL 4		0%	0%
MRP as percent reduction of submitted price with market size adjustment			
Where revenue < $12M and TCL 1, 2, 3 or 4		0%	0%
Where revenue $25M and TCL 1		0%	0%
Where revenue $25M and TCL 2		0%	0%
Where revenue $25M and TCL 3		0%	0%
Where revenue $25M and TCL 4		0%	0%
Where revenue $125M and TCL 1		16%	16%
Where revenue $125M and TCL 2		16%	16%
Where revenue $125M and TCL 3		16%	16%
Where revenue $125M and TCL 4		16%	16%

NOT AVAILABLE

Assumptions:
- Estimation of MRP would be determined from the stated indication.
- Submitted public price is the Maximum List Price (MLP) as price adjustments from the above calculations are applied to the MLP. (Note that the submitted price may be lower with the implementation of the draft Guidelines but the PEP cannot be calculated from the CADTH reports using an assumed lower price as the published CEA results depend on the submitted price. However, a lower submitted price will mean a lower price reduction is required to produce the same PEP.)

Interpretation of results

- The range in PEP price estimates (from $55.25 per mg through to $29.36 per mg) given the lack of a base case re-analysis from CADTH again shows how uncertain a price based on the PEP alone may be. However, in all scenarios examined here, the PEP estimate is above the submitted price.
- In this case study, the Reduction Floor has no influence on the estimate of the MRP.
- Price reductions become likely at revenue of $125M and beyond but are relatively modest.

Overall, given anecdotal evidence of the price reductions sought by the pCPA, these potential price reductions appear manageable and, thus it appears the MRP calculation algorithms themselves may have been unlikely to affect a launch decision had the 2020 draft Guidelines been in place at the time of the launch of osimertinib.

Darzalex (daratumumab)

Indication (coverage requested): In combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.

In combination with lenalidomide and dexamethasone

Item	CADTH Base Case	CADTH Best Case	CADTH Worst Case
ICER threshold - TCL 1 (a1)		200,000	200,000
ICER threshold - TCL 2, 3 and 4 (a2)		150,000	150,000
Incremental QALYs (b)		4	1
Incremental costs (c)		622,746	422,874
Treatment costs (d)		498,197	338,299
Submitted public price (e) - $/mg		5.98	5.98
PharmacoEconomic Price - PEP if TCL 1 (e*(a1*b+d-c/d) - $/vial		7.53	1.02
PharmacoEconomic Price - PEP if TCL 2, 3, or 4 (e*(a2*b+d-c/d) - $/vial		5.28	0.39
MRP as percent reduction of submitted price with floor test			
If TCL 1		0%	20%
If TCL 2		12%	30%
If TCL 3		12%	40%
If TCL 4		12%	50%
MRP as percent reduction of submitted price with market size adjustment			
Where revenue < $12M and TCL 1, 2, 3 or 4		0%	0%
Where revenue $25M and TCL 1		0%	10%
Where revenue $25M and TCL 2		6%	16%
Where revenue $25M and TCL 3		6%	21%
Where revenue $25M and TCL 4		6%	26%
Where revenue $125M and TCL 1		16%	27%
Where revenue $125M and TCL 2		23%	33%
Where revenue $125M and TCL 3		23%	39%
Where revenue $125M and TCL 4		23%	45%

In combination with bortezomib and dexamethasone

Item	CADTH Base Case	CADTH Best Case	CADTH Worst Case
ICER threshold - TCL 1 (a1)		200,000	200,000
ICER threshold - TCL 2, 3 and 4 (a2)		150,000	150,000
Incremental QALYs (b)		2	1
Incremental costs (c)		189,690	178,583
Treatment costs (d)		151,752	142,866
Submitted public price (e) - $/mg		5.98	5.98
PharmacoEconomic Price - PEP if TCL 1 (e*(a1*b+d-c/d) - $/vial		12.06	6.12
PharmacoEconomic Price - PEP if TCL 2, 3, or 4 (e*(a2*b+d-c/d) - $/vial		8.67	4.22
MRP as percent reduction of submitted price with floor test			
If TCL 1		0%	0%
If TCL 2		0%	29%
If TCL 3		0%	29%
If TCL 4		0%	29%
MRP as percent reduction of submitted price with market size adjustment			
Where revenue < $12M and TCL 1, 2, 3 or 4		0%	0%
Where revenue $25M and TCL 1		0%	0%
Where revenue $25M and TCL 2		0%	15%
Where revenue $25M and TCL 3		0%	15%
Where revenue $25M and TCL 4		0%	15%
Where revenue $125M and TCL 1		16%	16%
Where revenue $125M and TCL 2		16%	33%
Where revenue $125M and TCL 3		16%	33%
Where revenue $125M and TCL 4		16%	33%

NOT AVAILABLE

Assumptions:
- Estimation of MRP would be determined from the stated indication.
- Treatment cost is not reported in the CADTH reports so treatment cost is assumed to be a constant proportion (80%) of the incremental cost.
- Submitted public price is the Maximum List Price (MLP) as price adjustments from the above calculations are applied to the MLP.

Interpretation of results

- The range in PEP price estimates (from $12.06 per mg through to 39c per mg – a 93% price reduction) given the lack of a base case re-analysis from CADTH shows how uncertain a price based on the PEP alone may be.
- The Reduction Floor reduces this possible variation substantially resulting in prices ranging from no reduction relative to the submitted price (assumed to be the MLP) to a 50% reduction.
- Given the first $12M of revenue may be earned at the MLP, the market size adjustment also significantly attenuates the possible range of required price reductions from none through to a worst case of 15% -26% at revenue of $25M (depending on the comparator) and a worst case of 33% to 45% at revenue of $125M (depending on the comparator).

Overall, given anecdotal evidence of the price reductions sought by the pCPA, these potential price reductions appear manageable and, thus it appears the MRP calculation algorithms themselves may have been unlikely to affect a launch decision had the 2020 draft Guidelines been in place at the time of the launch of osimertinib.

Blincyta (blinatumomab)

Estimation of MRP

Indication (coverage requested): For the treatment of pediatric patients with Philadelphia chromosome-negative relapsed or refractory B precursor acute lymphoblastic leukemia (ALL).

And for the treatment of all adult patients with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL), including those who have had one prior line of therapy (i.e., adult patients who are refractory or patients who are in first or later relapse)

Item	CADTH Base Case	CADTH Best Case	CADTH Worst Case
ICER threshold - TCL 1 (a1)		200,000	200,000
ICER threshold - TCL 2, 3 and 4 (a2)		150,000	150,000
Incremental QALYs (b)		1	0
Incremental costs (c)		158,224	158,270
Treatment costs (d)		154,919	154,964
Submitted public price (e) - $/vial		2,987.26	2,987.26
PharmacoEconomic Price - PEP if TCL 1 (e*(a1*b+d-c/d) - $/vial		2,674.42	553.14
PharmacoEconomic Price - PEP if TCL 2, 3, or 4 (e*(a2*b+d-c/d) - $/vial		1,989.88	398.92
MRP as percent reduction of submitted price with floor test			
If TCL 1		10%	20%
If TCL 2		30%	30%
If TCL 3		33%	40%
If TCL 4		33%	50%
MRP as percent reduction of submitted price with market size adjustment			
Where revenue < $12M and TCL 1, 2, 3 or 4		0%	0%
Where revenue $25M and TCL 1		5%	10%
Where revenue $25M and TCL 2		16%	16%
Where revenue $25M and TCL 3		17%	21%
Where revenue $25M and TCL 4		17%	26%
Where revenue $125M and TCL 1		22%	27%
Where revenue $125M and TCL 2		33%	33%
Where revenue $125M and TCL 3		35%	39%
Where revenue $125M and TCL 4		35%	45%

Assumptions:

- Estimation of MRP would be determined from the adult indication given its likely greater prevalence.
- Treatment cost is not reported in the CADTH reports but median treatment cycles and cycle cost is reported for the submitted base case. Treatment costs under the best and worst cases are assumed to be the same constant proportion of the incremental cost calculated from the median cycles and cycle costs reported for the submitted base case.
- Submitted public price is the Maximum List Price (MLP) as price adjustments from the above calculations are applied to the MLP. (Note that the submitted price may be lower with the implementation of the draft Guidelines but the PEP cannot be calculated from the CADTH reports using an assumed lower price as the published CEA results depend on the submitted price. However, a lower submitted price will mean a lower price reduction is required to produce the same PEP.)

Interpretation of results

- The range in PEP price estimates (from $2,674.42 through to $398.92 per vial – an 87% price reduction) given the lack of a base case re-analysis from CADTH shows how uncertain a price based on the PEP alone may be.
- The Reduction Floor reduces this possible variation significantly resulting in prices ranging from 10% reduction relative to the submitted price (assumed to be the MLP) to a 50% reduction.
- Given the first $12M of revenue may be earned at the MLP, the market size adjustment also significantly attenuates the possible range of required price reductions from 5% through to 26% (at revenue of $25M) and 22% to 45% (at revenue of $125M).
- The results also indicate that the potential price reduction required is significantly affected the TCL classification of the drug.

Overall, given anecdotal evidence of the price reductions sought by the pCPA, these potential price reductions appear manageable and, thus it appears the MRP calculation algorithms themselves may have been unlikely to affect a launch decision had the 2020 draft Guidelines been in place at the time of the launch of osimertinib.

The degree of variation in price reductions likely as a result of the TCL determination and the level of unknowns surrounding this determination in the short term would, however, likely introduce a significant level of uncertainty that could lead to decisions not to, or delay, launch.

Unituxiini (dinutuximab)

Estimation of MRP

Indication (coverage requested): for use in combination with GM-CSF, IL-2 and Retinoic acid (RA) for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multi-agent, multimodal therapy (a very small group of patients numbering around 25 to 35 a year in Canada).

Item	CADTH Base Case	CADTH Best Case	CADTH Worst Case
ICER threshold - TCL 1 (a1)	200,000		
ICER threshold - TCL 2, 3 and 4 (a2)	150,000		
Incremental QALYs (b)	5		
Incremental costs (c)	347,793		
Treatment costs (d)	313,014		
Submitted public price (e) - $/vial	12,850.00		
PharmacoEconomic Price - PEP if TCL 1 (e*(a1*b+d-c/d) - $/vial	37,490.01		
PharmacoEconomic Price - PEP if TCL 2, 3, or 4 (e*(a2*b+d-c/d) - $/vial	27,760.56		
MRP as percent reduction of submitted price with floor test		NOT AVAILABLE	NOT AVAILABLE
If TCL 1	0%		
If TCL 2	0%		
If TCL 3	0%		
If TCL 4	0%		
MRP as percent reduction of submitted price with market size adjustment			
Where revenue < $12M and TCL 1, 2, 3 or 4	0%		
Where revenue $25M and TCL 1	0%		
Where revenue $25M and TCL 2	0%		
Where revenue $25M and TCL 3	0%		
Where revenue $25M and TCL 4	0%		
Where revenue $125M and TCL 1	16%		
Where revenue $125M and TCL 2	16%		
Where revenue $125M and TCL 3	16%		
Where revenue $125M and TCL 4	16%		

Assumptions:

- Treatment cost is not reported in the CADTH reports but the individual costs of the combination treatment are itemised for a full 6 cycles of treatment. Thus the proportion that dinutuximab (90%) makes up of these costs (less isotretinoin) is used to estimate treatment costs as a proportion of incremental costs.
- Submitted public price is the Maximum List Price (MLP) as price adjustments from the above calculations are applied to the MLP. (Note that the submitted price may be lower with the implementation of the draft Guidelines but the PEP cannot be calculated from the CADTH reports using an assumed lower price as the published CEA results depend on the submitted price. However, a lower submitted price will mean a lower price reduction is required to produce the same PEP.)

Interpretation of results

- The range in PEP price estimates (from $27,761 through to $37,490 per vial) shows the level of variation possible from TCL classification is non-trivial. However, in both scenarios examined here, the PEP estimate is above the submitted price.
- In this case study, the Reduction Floor has no influence on the estimate of the MRP.

- Price reductions become likely at revenue of $125M and beyond but are relatively modest.

Overall, given anecdotal evidence of the price reductions sought by the pCPA, these potential price reductions appear manageable and, thus it appears the MRP calculation algorithms themselves may have been unlikely to affect a launch decision had the 2020 draft Guidelines been in place at the time of the launch of osimertinib.

Tagrisso (osimertinib)

Estimation of MRP

Indication (coverage requested): For the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) mutations.

Compared with gifitinib

Item	CADTH Base Case	CADTH Best Case	CADTH Worst Case
ICER threshold - TCL 1 (a1)		200,000	200,000
ICER threshold - TCL 2, 3 and 4 (a2)		150,000	150,000
Incremental QALYs (b)		0	0
Incremental costs (c)		142,401	141,598
Treatment costs (d)		131,147	130,408
Submitted public price (e) - $/mg		3.68	3.68
PharmacoEconomic Price - PEP if TCL 1 (e*(a1*b+d-c/d) - $/mg		2.32	1.94
PharmacoEconomic Price - PEP if TCL 2, 3, or 4 (e*(a2*b+d-c/d) - $/mg		1.66	1.38
MRP as percent reduction of submitted price with floor test			
If TCL 1		20%	20%
If TCL 2		30%	30%
If TCL 3		40%	40%
If TCL 4		50%	50%
MRP as percent reduction of submitted price with market size adjustment			
Where revenue < $12M and TCL 1, 2, 3 or 4		0%	0%
Where revenue $25M and TCL 1		10%	10%
Where revenue $25M and TCL 2		16%	16%
Where revenue $25M and TCL 3		21%	21%
Where revenue $25M and TCL 4		26%	26%
Where revenue $125M and TCL 1		27%	27%
Where revenue $125M and TCL 2		33%	33%
Where revenue $125M and TCL 3		39%	39%
Where revenue $125M and TCL 4		45%	45%

Compared with ofatinib

Item	CADTH Base Case	CADTH Best Case	CADTH Worst Case
ICER threshold - TCL 1 (a1)		200,000	200,000
ICER threshold - TCL 2, 3 and 4 (a2)		150,000	150,000
Incremental QALYs (b)		0	0
Incremental costs (c)		138,459	137,686
Treatment costs (d)		130,882	130,152
Submitted public price (e) - $/mg		3.68	3.68
PharmacoEconomic Price - PEP if TCL 1 (e*(a1*b+d-c/d) - $/mg		2.26	1.88
PharmacoEconomic Price - PEP if TCL 2, 3, or 4 (e*(a2*b+d-c/d) - $/mg		1.64	1.36
MRP as percent reduction of submitted price with floor test			
If TCL 1	NOT AVAILABLE	20%	20%
If TCL 2		30%	30%
If TCL 3		40%	40%
If TCL 4		50%	50%
MRP as percent reduction of submitted price with market size adjustment			
Where revenue < $12M and TCL 1, 2, 3 or 4		0%	0%
Where revenue $25M and TCL 1		10%	10%
Where revenue $25M and TCL 2		16%	16%
Where revenue $25M and TCL 3		21%	21%
Where revenue $25M and TCL 4		26%	26%
Where revenue $125M and TCL 1		27%	27%
Where revenue $125M and TCL 2		33%	33%
Where revenue $125M and TCL 3		39%	39%
Where revenue $125M and TCL 4		45%	45%

Assumptions:

- Treatment cost is not reported in the CADTH reports but median treatment duration is provided for the submitted base case. Together with estimated monthly cost, a cost of treatment with osimertinib is estimated. This cost, as a proportion of incremental costs in the submitted base case, is assumed to be constant in all other cases.
- Submitted public price is the Maximum List Price (MLP) as price adjustments from the above calculations are applied to the MLP. (Note that the submitted price may be lower with the implementation of the draft Guidelines but the PEP cannot be calculated from the CADTH reports using an assumed lower price as the published CEA results depend on the submitted price. However, a lower submitted price will mean a lower price reduction is required to produce the same PEP.)

Interpretation of results

- The range in PEP price estimates (from $2.32 through to $1.36 per mg) given the lack of a base case re-analysis from CADTH again shows how uncertain a price based on the PEP alone may be.
- The Reduction Floor reduces this possible variation substantially resulting in prices ranging from a 20% reduction relative to the submitted price (assumed to be the MLP) to a 50% reduction.
- Given the first $12M of revenue may be earned at the MLP, the market size adjustment also significantly attenuates the possible range of required price reductions from none through to 26% (at revenue of $25M) and 45% (at revenue of $125M).
- The results also indicate that the potential price reduction required is significantly affected the TCL classification of the drug.

Overall, given anecdotal evidence of the price reductions sought by the pCPA, these potential price reductions appear manageable and, thus it appears the MRP calculation algorithms themselves may have been unlikely to affect a launch decision had the 2020 draft Guidelines been in place at the time of the launch of osimertinib.

The degree of variation in price reductions likely as a result of the TCL determination and the level of unknowns surrounding this determination in the short term would, however, likely introduce a significant level of uncertainty that could lead to decisions not to, or delay, launch.

Other observations

- The 2020 draft Guidelines use ICER thresholds that bear no relationship with those implicitly used by CADTH. It is widely accepted anecdotally that CADTH uses a threshold of $100,000 for oncology drugs and $50,000 for other technologies when proclaiming the price of a technology is not at a level considered cost effective. It is odd, therefore, that in the process of proposing new draft Guidelines that the ICER thresholds used across the Canadian health system are not proposed to be congruent with one another.

- This analysis did not try to determine into which TCL the drug under analysis would fall. The reason for this is that the definitions of the TCL are open to significant variation in interpretation. For example:

  TCL 1 includes ". . . is the first medicine . . . that effectively treats a particular illness or effectively addresses a particular indication in a clinically impactful manner . . . " and, therefore, leaves a question mark over impactful treatments that are used in an indication for a sub-group of patients (defined, potentially, by a genetic marker) that gain no benefit from treatments already available for the indication.

  TCL 1 notes that "A high QALY gain is normally associated with medicines at this level." TCL 2 also notes "A high QALY gain is normally associated with medicines at this level." But how high in each case?

  The difference in ICER threshold between TCL 1 and 2 is significant and can result in non-trivial differences in PEP estimates.

- The creation of different TCLs will create a great deal of uncertainty over how the PMPRB will classify drugs as, for the short term at least, there will be no history on which stakeholders may base their judgements. Key stakeholders needing to understand this judgement include both manufacturers making decisions to bring products to market and the pCPA (or payer negotiators) who must attempt to make pricing decisions that in the medium term are not higher than those established on PMPRB review. The pCPA may address this uncertainty through two means: either delaying its negotiations where it has the greatest uncertainty or by negotiating higher price reductions than it might have otherwise. Either way, the uncertainty introduced in the short term may manifest itself as private decisions by manufacturers to not launch in the Canadian market.

Appendix C

November 2019 Draft Guidelines Submission

PMPRB Guideline Submission February 14th, 2020

Thank you for the opportunity to provide feedback on the draft Guidelines published in late November 2019.

We, the signatories to this submission, will provide below some background to our deliberations to set the context though which we considered the Guidelines, provide case studies for your review (attached), provide comments about technical areas of concern about the Guidelines, describe substantive issues from an oncology specific perspective with the Guidelines and provide recommendations to remedy those concerns.

Background

We are aware of the challenges of a duel federal/provincial jurisdiction for aspects of healthcare for people across Canada.

We are also aware that there are inequities in coverage for medications across the country due to several factors. Public systems are the responsibility of provinces and territories and of course each has its own economic engine, priorities, demographics and other factors that drive decisions about how much to spend, what to fund and what funding models to implement. In addition, employers, unions and individuals who can afford them have private plans that provide additional access.

Patients understand that this is the construct we have. We understand that public plans cannot afford to provide access to all drugs that we might need although we trust that they will use instruments that will help make fair, objective and evidence-based choices. We want a sustainable system; we want the prices of drugs to permit sustainability. This is no doubt the appeal of a universal single payer pharmacare plan.

Patient groups continue to support health technology assessment agencies, CADTH and INESSS ,and also pCPA. As for PMPRB, over 20 years ago, the Canadian Treatment Action Council , a

national patient driven HIV organization, chaired by Louise Binder, a representative of one of the signatories to this submission, advocated strongly to the PMPRB and the then federal Minister of Health, (including holding a public protest) that the Regulations for PMPRB be amended to remove the U.S. from the basket as an outlier, with high drug prices, and with health policies inconsistent with our health system. Finally, this is happening.

Patient organizations support the reassessment of the current basket of reference countries proposed for PMPRB consideration.

It is also important in our view to remember the history of cancer management in Canada:

- In 2007 the House of Commons Standing Committee on Health heard evidence that cancer treatments required their own health technology assessment process to ensure that value is analyzed based on factors relevant to that complex group of diseases. The Committee agreed with these recommendations. The result of those hearings was the creation of pCODR with a four-part deliberative Framework as its HTA process.
- The federal government also created a cancer strategy stewarded by the Canadian Partnership Against Cancer.
- Provinces have cancer agencies to manage cancer generally, including drug reimbursement, separately from other treatments.

The statistics regarding cancer certainly make the case for this specific focus on cancer:

- It is the number 1 cause of death in Canada.
- It is estimated that 1 of 2 people in Canada will be diagnosed with cancer in their lifetime.
- 1 in 4 will die from it, or 821,000 in Canada.

This is a huge public health issue that requires a discreet policy approach, as the governments have recognized.

In addition, as we know, there is not just one type of cancer, one stage of cancer or one cause of cancer:

- There are cancers that are uncommon and those that are more common.
- There are cancers for which research has found genetic links that inform prevention and treatment and those that have not.
- There are cancers that can be cured.
- There are cancers that can be effectively and have been transformed into chronic illnesses with newer, more effective treatments; yet, there are many that continue to be a certain death sentence within months of diagnosis.

Breast cancer: The most common cancer among women, both young and older people alike, is breast cancer. In 2019, 26,900 women were diagnosed with breast cancer and 5,000 will die of this disease. 230 men will also be diagnosed with breast cancer. Among women, between 5 and 10% of breast cancers are thought to be hereditary. The BRCA1 and BRAC2 have been known to be linked with a higher link of breast cancer. More recently, a study in 2017 found 72 new genetic mutations linked to breast cancer and now under study.

Colorectal cancer: Colorectal cancer is the number 2 leading cause of death from a cancer. 50% of cases are diagnosed at stage III and IV and 9600 died of this cancer in 2019.

Lung cancer: Lung cancer has a 29,300 incidence and 21,000 will die each year in Canada. It is the leading cause of cancer deaths for males and females at 25 % and 26 % respectively. Contrary to public opinion, it is not just a disease of those who smoke. Unlike breast cancer, no genetic links have been discovered related this disease. There are certain "signatures" within the lung cancer cell that determine which oral cancer therapies to use. It has a 19% five year survival rate compared to 93 % in prostate cancer, 88% in breast and 65% in colorectal.

Uncommon cancers: There are also uncommon cancers like gastrointestinal stromal tumours (GIST) with unknown prevalence and incidence levels in Canada but estimated at about 400 cases. Genetic testing is recommended to guide treatment decisions for high risk resected and advanced GIST

Paediatric cancers: In young people, approximately 3,800 children, adolescents and young adults aged 0 to 29 years of age are diagnosed with cancer each year in Canada in 2019. 1,500 children and adolescents aged between 0 and 19 were diagnosed with cancer in Canada. Cancer is the second most common cause of death for children in the developed world, after accidents. 416 Canadian children will die of cancer every year. The five-year survival rate for Canadian children has improved from 71% to 82% due to access to new treatments. Without treatment these cancers are fatal.

In our submission the PMPRB, as another agency of the federal government, must recognize that government policy has determined that oncology is a discreet group of diseases for public policy purposes. The signatories to this submission strongly support public policy in this regard.

Until the Guidelines were issued in late November 2019, patient groups had no defined concrete formula or processes by which to determine whether the planned changes will consider public policy regarding oncology and, therefore, whether it will be a good public policy instrument. We do not want another health technology instrument that is less robust than those we presently have.

In order to ensure an objective, evidence based and expert analysis of the Guidelines, we asked an external consultant to assist us. Specifically we asked him to look at a number of oncology drugs for different types of cancer that have been reviewed by pCODR fairly recently and to compare the outcomes they received through that process with the outcomes we can predict they would have had under the proposed Guidelines with the information available to us.

Case studies

Attached are the six case studies analyzed by the health economics expert. We chose these because they are drugs that have been reviewed recently by pCODR so we have numbers for them – at least those that are in the public domain.

Conclusions

It is clear that oncology needs its own approach in these Guidelines, as the federal and provincial governments have recognized in other health policies. It is clear that this approach must be flexible enough to recognize the differences between uncommon and more common cancers, difference stages of cancer, genetic factors, paediatrics versus adults, comorbidities, Indigenous populations and social determinants of health, to name a few. This blunt instrument may be workable for some diseases. The case study analysis clearly demonstrates that we need a much more nuanced, flexible and pragmatic instrument is required for cancers.

In two cases the impact of the Guidelines is minimal in terms of pricing changes required and probably will not change the decision about whether or when the drug will come to market in Canada.

In the vast majority of cases, however, the use of this one blunt health technology instrument, the single criterion of an ICER, will generally not make it a practical economic business decision to bring this drug to Canada, or at least not to put it high on the list for applications relative to other countries for market entry.

CADTH's deliberative framework for oncology drugs, with four considerations, including clinical benefit, cost effectiveness, patient values and feasibility of adoption, has recognized this nuanced, flexible and pragmatic health technology assessment required for oncology drugs. This is a recognition that there are limitations of using a single outcome measure for economic evaluation, since doing so that important health consequences are excluded. INESSS also takes into account public and patient values into its health technology assessment considerations.

Recommendation #1

The Guidelines be amended to adopt explicitly the CADTH pCODR deliberative framework for oncology health technology assessment and remove any specific reference to an ICER.

Recommendation #2

The Guidelines be amended to provide that PMPRB's public decision will provide information that the analysis has either met the PMPRB threshold and is not excessive or that it has not met the PMPRB threshold or other CADTH analysis and is excessive. No specific economic data or numbers supporting this decision will be made public by PMPRB. This will ensure that the public Canadian price will not put at risk the U.S. market such that companies will decline to enter, or delay, the Canadian market for that reason.

Recommendation #3

The Guidelines be amended to provide for ongoing monitoring and evaluation by a multi-stakeholder Committee and a publicly issued annual report of findings of this Committee. At least two patient group representatives chosen by the patient community, with one from the cancer community, will be included.

Recommendation #4

No Guideline finalization should take place until a full consultation is undertaken with Quebec stakeholders including patient groups and patients with all documents and consultations taking place in both Official languages.

Recommendation #5

No Guideline finalization should take place until a full consultation is undertaken with Indigenous stakeholders *i.e.* First Nations, Metis and Inuit including patient groups and patients following a process of their choosing.

Technical issues to be resolved

1. PMPRB states that it will rely on the base case reanalysis conducted by the public agency (i.e. CADTH and/or INESSS). pCODR does not presently generally do a base case reanalysis and INESSS does one in some cases but not all. This will require coordination amongst the agencies.

2. pCODR builds in the price for companion diagnostics. The manner in which this will be analyzed and taken into account by PMPRB must be clarified and should be described in the Guidelines.
3. pCODR does not do weighted averages for subgroups. PMPRB requires these. This will require coordination between the agencies for resolution.

Martine Elias, Chair
CONECTed

Kathleen Barnard, President and Founder
Save Your Skin Foundation

Elizabeth Lye, Director of Research & Programs
Lymphoma Canada

Martine Elias, Executive Director:: Directrice Générale
Myeloma Canada

Christina Sit, Patient Advocate
Lung Cancer Canada

Appendix D

Protecting Canadians from Excessive Drug Prices: Consulting on Proposed Amendments to the Patented Medicines Regulations – 2017 Submission

Recommendations on Proposed Amendments to the Patented Medicines Regulations

June 28, 2017

Endorsed By:

Canadian Cancer Survivor Network

Canadian Psoriasis Network

Réseau canadien du psoriasis

Canadian Spondylitis Association

CNETS Canada

Carcinoid-NeuroEndocrine Tumour Society Canada

hepcbc

Lung Cancer Canada

Awareness. Support. Education.

Lymphoma Canada

Melanoma Network of Canada

Sun Safe. Sun Aware.

Myélome Canada

Myeloma Canada

Rethink breast cancer

save your skin Foundation

La Fondation sauve ta peau

Ontario Caregiver Coalition

Coalition des aidantes et aidants naturels de l'Ontario

Schizophrenia Society of Ontario

A Reason to Hope

SCDAC AAFC

SCAGO

Sickle Cell Awareness Group of Ontario

CONECTed

Collective Oncology Network for Exchange, Cancer Care, Innovation, Treatment Access & Education

BREATHE

the lung association

ONTARIO

A. INTRODUCTION

Our health care system is complex; no one would argue to the contrary. There are many key decision makers at either federal, national or provincial levels that are responsible for the health care services Canadians receive from coast to coast to coast. Health Canada holds different responsibilities influencing the landscape of our health care system, including drug safety, quality and effectiveness. In addition, they play an important role with respect to drug pricing. We, as patient organisations, recognise the regulations overseeing drug pricing need to be re-evaluated, especially given the changes in our ecosystems since the inception of these regulations. Moving forward, changes are necessary to ensure Canadians get the best possible and timely access to health care resources while ensuring sustainability of our health care system for generations to come. We know the people who work at Health Canada also have the same vision. We are grateful to all those involved in seeking the input of groups like ours and other stakeholders on protecting Canadians from excessive drug prices through the consultation on the proposed amendments to the patented medicines regulations. We believe our health care system must prepare for a significant paradigm shift and welcome opportunities to share our thoughts on what needs to be done by collaborating with all stakeholders involved in making our health care system the best it can be.

Background

Drug Systems Structure in Canada

Canada has a unique health care system because of the division of responsibilities between the federal and provincial/territorial governments. The federal *Canada Health Act* promises eligible people in Canada access to doctors and hospitals. Incidentally this means free drugs in hospitals but only for those determined by hospital drug formularies. The provinces and territories have the responsibility to create public drug funding mechanisms and each has done so based on relevant criteria for each, including the economic engine of the province, competing interests for public funds, population demographics and needs and other relevant factors. Thus, public plans are different across each province/territory.

The collective public systems cover approximately 60 per cent of drug expenditures and the private sector covers the rest, mainly through employer-sponsored benefit plans provided through private insurance companies. Some people purchase individual private plans, while others have no coverage (sometimes referred to as “the working poor”), are underinsured (people with inadequate private coverage) or are “theoretically insured” (those who are eligible for public reimbursement plans but cannot afford the deductibles or co-pays to access them).

Recent Trends in Health

While health costs have always been a large part of every provincial/territorial budget, the cost of the drug portion of the overall health budget is growing as we discover the causes of new “rare” diseases, learn how to cure diseases such as Hepatitis C, manage a disease like HIV with lifetime treatments and more recently make huge breakthroughs in cancer treatment, referred to as personalized medicine, precision medicine and immuno-oncology.

While science is making headway by leaps and bounds, the economic engines of our country are not keeping pace. There are also increased competing demands on public dollars, our population is aging and the number of people working is declining. There are other factors

including global competition, the environment and new work paradigms. This problem is not unique to Canada but as stated at the outset, the federal/provincial/ territorial split in the health mandate is unique.

Thus, governments are talking more than ever about health care sustainability, affordability and public/private partnerships in health. Specifically, the federal government has adopted the three "A"s of health policy: affordability, accessibility and the appropriate use of prescription drugs.

Regulatory Roles in Health including the Patented Medicine Prices Review Board's (PMPRB) Role

There are several regulatory checks and balances in decisions about health interventions. The federal role through Health Canada includes ensuring that products entering Canada are safe, effective and of good quality. PMPRB monitors that the proposed ex-factory price at which a drug will enter Canada is not excessive, as part of its consumer protection role. The Canadian Agency for Drugs and Technologies in Health (CADTH) recommends to public payers whether a product is of value to be paid for out of the public purse for eligible people. L'Institut national d'excellence en sante et en service sociaux (INESSS) has the same mandate for Quebec. The pan-Canadian Pharmaceutical Alliance (pCPA) negotiates a price for the public plans. Cancer agencies provide advice on cancer drugs. Each province determines whether and/or when to add a product to its public reimbursement plan. Private insurers recommend and offer plan designs that are competitive for employers. They work from the PMPRB price but have also negotiated lower prices with pharmaceutical companies in several cases. Individuals pay for drugs they can afford but are not covered for them by private or public plans.

Health Canada and PMPRB have determined within this environment that it is time to do a review of drug prices based on a mandate from the federal Minister of Health to make recommendations about what to do about the fact that drug prices in Canada are "too high". This conclusion is based primarily on an analysis that says that Canada is paying the second highest drug prices overall of the seven countries with which it has been comparing itself. The drug budget is generally quoted as being 16 per cent of the total health budget including generic drugs and over-the-counter medicines. Depending on whose numbers you accept, innovative drug prices have been rising, stable, or declining. Another reason for this review is the fact that research and development has been going down, notwithstanding a commitment when the *Patent Act* sections on pricing were introduced that it would be at 10 per cent and has dropped to about 4 per cent. There are numerous reasons for this also based on whose narrative you accept.

The above-signed patient groups have analyzed the proposed regulatory changes and have the following recommendations to make:

Summary of Recommendations

- Removal of the pharmacoeconomic evaluation analysis as a mandatory process from the Regulations and to move it to the Guidelines along with other listed relevant factors to be considered. We believe this is appropriate because the "willingness to pay" as defined in the document provided by Health Canada and the PMPRB for the use of pharmacoeconomic analysis varies among, and within, public payers, private insurers and individual payers. The decisions relevant to pharmacoeconomics must be left to those stakeholders who focus on specific patient populations and not be centrally

mandated by the federal government. The Regulations should therefore delete the use of a pharmacoeconomic analysis as mandatory but rather should move it to the Guidelines along with other discretionary factors that may be pertinent depending on the circumstances of the product being reviewed as being an excessive price to enter the Canadian market.

- The definition of "size of the market" needs to be clarified to clearly differentiate between current number of patients versus expected patients to be put on the patented medicine.

- While we have no objection to Canada considering GDP to determine an excessive ex-factory market entry price, we submit that including other measures such as overall percentage of dollars spent on prescription medicines relative to health outcomes, reduction of hospitalization or other metrics are also relevant and useful. Unfortunately, the issue of silo budgeting, and looking at each piece of the health budget relative to outputs rather than holistically in relationship to their impact on health outcomes, is a serious fundamental flaw with our entire health care system vision and structure.

- pCPA should be mandated by the Council of the Federation to negotiate agreements based on such innovative contract approaches as pay for performance, risk sharing agreements and other innovative contractual designs, rather than solely on a negotiated price, since that approach will truly reduce prices and the overall drug budget.

- Government policies should be created that ensure that all savings from drug pricing reductions are returned to the public health budget, or become an automatic rebate to employers in the case of private group insurance plans for use to augment drug coverage for employees with life-threatening or serious illnesses, or become an automatic rebate to individuals with private individual coverage.

- During the consultations, we suggested other relevant factors be included. With respect to the proposed list of 12 comparator countries, the federal government should ensure that all factors are considered and compared and that these be made transparent. These include: private/public insurance drug split, health care delivery mix in each country, whether they have a robust Health Technology Assessment (HTA) process, overall health care system structure in each country, demographics of comparator country, price control strategy e.g. free price, maximum price or reimbursement price or a combination of these (we understand that all but Germany have a list price and all but Sweden, Norway and Japan have net prices), price control tools e.g. IRP, TRP, cost per QALY, Cost-plus /cost calculation, cost comparison, tendering or pricing negotiations, health systems data collection, monitoring and evaluation, time to market , what drugs are actually covered in those countries and the importance of wide and universal access, access to research and clinical trials and commitment to innovation and last but not least a measure of health outcomes (perhaps that from the WHO) in these countries need to be used in selecting comparator countries.

- Drugs for life-threatening diseases should receive special attention. The federal government should not use any comparator countries for drugs for life-threatening and serious diseases or conditions in the Regulations that delay market entry longer than Canada's present time to entry as Canadian patients cannot wait any longer than the

already lengthy delays experienced to obtain access to badly needed treatments. Thus, some or all of the comparator countries should be removed and replaced by more appropriate comparators. The federal government should not use any comparator countries for drugs for life-threatening and serious diseases or conditions in the Regulations that have less clinical trial access in these areas as clinical trials are an important means for access in Canada.

- The federal government should only select comparator countries that have comparable or better market entry times than Canada and comparable or better access to clinical trials as Canada.

- All analyses done in support of the Regulations should be made public.

- Additional factors that should be taken into account in selecting comparator countries include private/public insurance drug and health care delivery mix in each country, whether they have a robust HTA process, the entire health care system structure in each country, demographics of the country, price control strategy i.e. free price, maximum price or reimbursement price or a combination of these (we understand that all but Germany have a list price and all but Sweden, Norway and Japan have net prices), price control tools e.g. IRP, TRP, cost per QALY, cost-plus/cost calculation, cost comparison, tendering or pricing negotiations, time to market, health systems data collection, monitoring and evaluation, time-to-market, what drugs are actually covered in those countries and the importance of wide/universal access, access to research and clinical trials and commitment to innovation.

- There should be a clarification added to the proposed patented generic drug process explaining that the complaints process can be accessed by anyone.

- The definition of “indirect” discounts and rebates should be defined in the Regulation. The Regulation should clearly state how the information about indirect discounts and rebates will be used.

- Patient values must be added in the Regulation as an equally important factor for the PMPRB to consider as any others when determining whether a drug price is excessive since all Canadian governments have expressed that their health policies are based on patient-centred care.

- PMPRB and Health Canada should develop a rigorous monitoring and evaluation framework for the federal regulation of drug pricing designed with patient groups and reviewed annually and modified as required.

- An efficient, effective and mandatory dispute resolution mechanism within PMPRB for excessive pricing in the breakthrough drug category should be created within PMPRB such as a mandatory Alternative Dispute Resolution process with publicly published reasons for the decision as well as regular re-evaluation of a well-defined class of breakthrough drugs. These will address the core affordability problem of PMPRB.

- The *Patent Act* should be amended to delete the Consumer Price Index (CPI) as an automatic increase mechanism for therapies.

- The federal government must ensure that there are no unintended and unforeseen adverse consequences to public payers of a lower entry price into Canada for public and private payers by reducing the overall amount available to provincial/territorial payers for price negotiations before promulgating these Regulations. Such an adverse impact will mean less access to necessary medicines for eligible people in Canada and this is surely not the intention of the federal government.

In conclusion, we strongly believe when looking at drug pricing policy changes, the federal government should do so in the context of overall health outcomes, the impact on the entire health care system and employers. The real issue for many people in Canada is lack of access or inadequate access to necessary medicines. This is a problem worth solving. The main problem for the poor is the lack of funds to buy drugs or the inability to pay the deductibles, co-pays and other costs associated with being uninsured or underinsured. The federal government should set up a fund that these people can access across Canada to deal with this inequity in access. The federal government must recognize that where the impact of lowering the drug entry price in Canada by 20 per cent or more is less access or delayed access for patients, the above-signed patient groups and the patients they represent will not support it.

The federal government must show leadership in health by convening a multi-stakeholder group including meaningful patient group representation to find a common vision for the health care system founded on value-based health outcomes and to determine how to collaborate to achieve that goal together.

B. REVIEW OF THE QUESTIONS POSED BY HEALTH CANADA

1. Introduction

Drugs treat chronic conditions, improve, and save lives. Having access to drugs, new and old, should not be considered a privilege, but a right of every Canadian. Our health care system, although not perfect, is one of the most important characteristics of our country, of who we are, and what we represent.

The goal of our collective governments should be to look at ways to improve how we provide and pay for health care with a view to improving health outcomes and making our system sustainable for generations to come.

Protecting consumers from excessive drug prices is a critical part of ensuring this goal is attainable. Through the PMPRB, we believe the federal Minister of Health has played, and should continue to play, an important role in ensuring that drugs are not brought into Canada at an excessive price.

The ecosystem for pharmaceutical therapies in Canada has changed since the adoption of Bill C22 (the *Patent Act*) and since the creation of the PMPRB in 1987. Amending these *Regulations* is necessary to modernise our drug pricing system. However, we firmly believe that the following principles developed by patient groups must be maintained when considering or making changes to drug pricing regulations to protect all Canadians:

- **Protect** or **improve** existing individual access to therapies at or above their current level.
- **Safeguard and improve access** to medically necessary therapies for all residents of Canada regardless of ability to pay or place of residency.
- **Ensure universality and equality** that recognizes diversity in all its forms and accommodation for disability.
- **Brings cutting-edge pharmaceutical research** to Canada so Canadians can benefit from these research programs that would otherwise not be accessible.
- **Recognize** the discrete needs of people with life-threatening and serious debilitating illnesses that significantly impact their and their caregivers' quality of life.
- **Accept, assess and value** real-world evidence in determining therapeutic value.
- **Reinvest** pharmaceutical system savings back into the pharmaceutical budget to provide increased access to therapies.
- **Build** on the foundation of health care mechanisms and systems already in place.
- **Develop** value-based drug pricing contracts, including systems for sharing data and other relevant information.
- **Analyze** the overall value and broader socio-economic impact of a drug, including cost savings in other parts of the health care budget.
- **Expand** health technology assessment processes to measure the value of all components of the health care budget.

With these principles in mind, the above-signed patient organisations are pleased to provide feedback to the proposed amendments to the Regulations promulgated pursuant to the *Patent*

Act. We appreciate Health Canada for reaching out to stakeholders to be involved in a meaningful way in this consultation process.

2. **General Comment**

The *Patent Act* is the governing federal legislation under which all Regulations and Guidelines related to excessive drug pricing are made. They are "handmaidens" to the *Patent Act*, defining how the Act will be administered. Thus, when looking at each Regulation and Guideline an overarching question is whether the Regulation and Guideline proposed enable the law as defined in the *Patent Act*. If not, the Regulation or Guideline is *ultra vires*, outside the jurisdiction of the legislator or quasi-judicial administrative body to enact.

In addition, it is important to place the legislation in the context of other health regulatory systems in place in the public domain, i.e., Health Canada, CADTH, pCPA, cancer agencies and provincial/territorial drug plans. Each has its own mandate and PMPRB should not be duplicating the mandate of other systems.

It is also always important when reviewing solutions to a problem to ensure that the problem itself is clearly defined. There is much stated concern that Canada has the second highest drug pricing of the present seven comparator countries in the present Regulations. An April 2017 report by the PMPRB's National Prescription Drug Utilization System reports that for brand name drugs launched from 2009-2014, Canada was second lowest among the seven countries in the present Regulations.

Our understanding from PMPRB is that the main problem it faces is the ability of a patentee to use its monopoly position in the marketplace to charge prices that are very high and often outside the reach of payers. It has stated that this generally occurs for a very small number of the products it reviews, between 5 per cent and 10 per cent, those that are considered "breakthrough", also referred to as "blockbuster" or "niche buster". The Hepatitis C cure drugs are a recent example of this. This percentage may grow over time as this is where health care is heading, into the world of breakthrough cures through stem cells, biologics, immunotherapy, personalized medicine, biomarkers and away from dying in hospitals and long-term care homes, but their numbers will still be limited. In other cases, market forces naturally drive down the price of new drugs coming into Canada. Yet, the Regulation changes target all drugs, even those where the present system regulates price effectively. Thus, if this is the crux of the problem, the solution should address that problem.

It is also paramount in addressing the affordability portion of the three "A"s that there not be negative impacts on either or both of the other two: access or appropriate prescribing. In our submission, creating Regulations that address the real affordability problem, i.e., "excessive" prices for breakthrough drugs, will avoid these potential negative impacts.

3. Comments on Proposed Amendments

Proposal #1

I. The Pharmacoeconomic evaluation for the medicine and other medicines in the same therapeutic class in Canada and in countries other than Canada.

Consultation Question

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

We can only answer this question provisionally given that the scope of current pharmacoeconomic evaluation in Canada has been developed solely to provide advice and guidance to public payers and does not include private payers or people who pay out of pocket. In our submission, even if a pharmacoeconomic evaluation is one pertinent factor for consideration, it is by no means the only "important" factor (undefined and therefore subjective). Our general recommendations in addressing this question would be:

Recommendation:

1. Removal of the pharmacoeconomic evaluation analysis as a mandatory process from the Regulations and to move it to the Guidelines along with other listed relevant factors to be considered. We believe this is appropriate because the "willingness to pay" as defined in the document provided by Health Canada and the PMPRB for the use of pharmacoeconomic analysis varies among, and within, public payers, private insurers and individual payers. The decisions relevant to pharmacoeconomics must be left to those stakeholders who focus on specific patient populations and not be centrally mandated by the federal government. The Regulations should therefore delete the use of a pharmacoeconomic analysis as mandatory but rather should move it to the Guidelines along with other discretionary factors that may be pertinent depending on the circumstances of the product being reviewed as being an excessive price to enter the Canadian market.

Additional comments for consideration:

- PMPRB regulates drug list prices for all consumers, including employees and their dependants under health benefit plans offered by their employers or unions and managed by insurance companies, as well as individuals covered under public drug plans and people who pay out of pocket across Canada. Currently, pharmacoeconomics and the use of quality-adjusted life year (QALY) is used by CADTH to make recommendations to provincial drug plans under the lenses for which these provinces/territories reimburse drugs. These reviews are based on comparisons between the new technology and best practices already reimbursed in these provinces for defined and sometimes targeted populations (e.g. seniors, children) and other factors. This proposal for regulatory change incorporates the reviews/recommendations provided by CADTH which uses it solely for one sector of the consumer population while PMPRB is charged with providing a consumer protection service for all consumers. Will they be looking at one pharmacoeconomic evaluation for the public reimbursement population, one for the private payer population and one for the uninsured? If so, is that appropriate?

- The pan-Canadian Oncology Drug Review (pCODR), a programme of CADTH, is responsible for making coverage recommendations about cancer drugs to provincial and territorial drug plans. The pCODR review process is designed "to bring consistency and clarity to the assessment of cancer drugs" and emphasizes four dimensions of value in their decision criteria: clinical benefit, economic evaluations, patient-based values, and adoption feasibility.[1] The pCODR guidelines state that there is no weighting scheme for the criteria and no threshold that must be met for any single element of the review. Rather, decisions should be made based on the individual drug, disease, and context. In that regard, pCODR could be described as taking an implicit approach to decision-making. While there is no formal framework for the Common Drug Review (CDR), the CADTH programme for non-oncology drugs, there is similarly no weighting scheme to the criteria looked at through the CDR process. Proponents of implicit approaches to decision-making argue that some ambiguity is necessary to address the inherent complexity of priority setting, allowing for individual decision-makers to exercise appropriate contextual judgment.[2] It is not relying solely on a pharmacoeconomic assessment itself. In a recent study in Current Oncology a comparison of preferences from pCODR and from the Canadian public found that both groups were willing to forego some degree of efficiency (which QALYs alone provide) to prioritize specific patient characteristics. Thus, even pCODR recognizes that a pure pharmacoeconomic analysis based on QALYs is not appropriate across the board for all disease states and all populations and that some discretionary factors must be available to determine value in each situation.[3]

- Benefits of a drug can also vary between populations it is designed to treat. This is true for many disease states. This requires an examination of how the currently proposed Regulations will take that reality into account. For example, in the mental health area, response to psychiatric medications is highly individualized, variable and related to several factors such as genetics, age, sex and socio-economic factors. As a result, individuals often must try several medications before they find an effective treatment. The Regulations appear too rigid to take this into account.

- The proposed Regulations do not address cost benefit to determine an appropriate price for drugs that treat children, rare diseases and cancers. As presented, it has been conceded that it does not address children or rare diseases and in our submission, the same is true of cancers. In fact, given what we are learning about the complexity of each of the more than 200 cancers and the difference at each stage even within the same disease site of cancer, all cancers may well be defined as rare diseases.

- Determining a fair price for a drug is not a simple process. It implies that one must put a cost or value on human life. The introduction of a fixed cost per QALY threshold is very concerning for many reasons including:

    1. QALY measurements vary significantly between diseases (like cancer), patient population (pediatric vs elderly) and rare diseases. How could a fixed QALY threshold (line in the sand) reasonably address the value a drug can bring to a patient or his/her family. Patient values are totally divorced from such a process. From a patient's perspective, using QALYs is problematic as the methodology used to determine QALYs all too often fails to represent the real value a drug brings to a patient's health outcomes.

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[1] "The prioritization preferences of pan-Canadian Oncology Review members and the Canadian public: a stated-preferences comparison", *Curr. Oncol.* 2016 Oct.23 (5): 322-328, C. Skedgel PhD, p.322

[2] Ibid., p.322

[3] Ibid., p.327

2. In the case of people with disabilities, QALYs could create discrimination against their health status because treatments that restore people to their "normal" disabled states could be undervalued relative to those who return to a "healthy" state.

3. In Canada, as described above, QALYs are used by CADTH in its review process to make reimbursement recommendations to public provincial and federal drug plans. These recommendations are then used by the pCPA to negotiate listing agreements, presumably by reducing the QALYs to a more acceptable threshold, which is accomplished by reducing the drug price. These are non-transparent negotiations. PMPRB has said that "willingness to pay" is a relevant factor in the price of a drug. While we agree, each stakeholder's willingness to pay is different. In fact, even within the public payer group, each province/territory and the federal plans will have a different answer about willingness to pay depending on discreet factors within each jurisdiction including its tax base, its population base, its economic base, population demographics, other opportunity costs inside and outside health. Thus, the willingness to pay criterion is pertinent at the payer level not at the PMPRB level. Patient organisations believe that more power should be given to the provinces/territories to negotiate more acceptable drug prices by negotiating prices down, introducing pay for performance schemes, and investments in better disease management programs.

4. QALYs are calculated based on data obtained through clinical trial studies undertaken by drug manufacturers. These trials are highly controlled and patients are chosen with much care through strict inclusion and exclusion criteria. There should be more emphasis placed on what happens in the real world, once a drug has been used in a broader population. If QALYs are to be used in the decision-making process to determine an appropriate drug price entry into Canada, we urge Health Canada and payers to use real-world evidence to adjust price according to the value they provide as further evidence is gathered over time.

- The use of QALYs or other pharmacoenonomic methodologies as proposed in the consultation document, does not give us confidence that they will result in more equitable resource allocation or deliver better health care to Canadians. There must be a mechanism by which every dollar saved goes back to pay for better health care and access to treatments. This is achievable in the public sector but requires a change in government policy and processes. It is far more problematic in the private sector where there is no mechanism nor incentive nor commitment to reinvest drug plan cost savings into an employer-sponsored health plan.

- We do not understand how the drug pricing that assumes a reduction in list price would affect negotiations undertaken by the pCPA on behalf of the public drug plans. We do not know the extent to which private plan prices subsidize public plan prices. Given the lower prices for private payers, will pCPA have less of a buffer to negotiate listing agreements? If so, having lower prices would benefit private payers more so than the public drug plans. We are not privy to the information that would answer this question as it is in the purview of the pharmaceutical manufacturers. We strongly recommend that the federal government do its due diligence to ensure that there are not unforeseen unintended negative consequences for public payers in its price negotiations by starting at lower prices since patients will be the ultimate losers in that scenario as fewer drugs may well be available on public plans. If so, this would be exacerbated in provinces like Saskatchewan, British Columbia and Manitoba, where the design of their public plans is more broadly encompassing than in other provinces.

II. The size of the market for the medicine in Canada and in countries other than Canada and the Gross Domestic Product in Canada.

Consultation Question

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

No matter what, Canada will always be a small market for international pharmaceutical companies compared to many other countries. The smaller market opportunity we represent plays a significant role in what industry may or may not do when it comes to launching a drug in Canada. Of the 12 countries proposed for comparison, based on sales and price per product in 2012-2013, Canada will be compared to four bigger and eight smaller pharmaceutical markets. Thus, if size is an important factor, how well will this basket of countries represent good comparators?

In addition, there is lack of clarity about the definition of "size of the market". Does it refer only to current number of patients or does it refer to expected number of patients or both?

Recommendation:

1. The definition of "size of the market" needs to be clarified to clearly differentiate between current number of patients versus expected patients to be put on the patented medicine.

Additional comments for consideration:

- Market size is only one of the many factors that should be considered when determining whether a drug is priced excessively. It is not logical or feasible to assume that every time a new patented medicine comes into the market, everyone with the condition will suddenly switch to that new patented medicine (because patented and/or generic of same/similar therapeutic classes often already exist for current patients). Hence, market demand/value will likely stabilize the costs of newly patented medicines to market value, especially at the negotiation level, including pCPA and provincially.
- However, in the case of breakthrough medicines, such as hepatitis C (HCV) drugs, market size, especially the potential sudden increase in demand due to significant increased efficacy (i.e. a cure) or significant decrease in serious adverse events was apparently not anticipated. Many provinces and private payers arbitrarily put a non-evidence based requirement before providing treatment coverage. It is only very recently that negotiation of HCV drugs by pCPA broadened the coverage in some, but not all, of the provinces. As Canada's health care delivery is at the provincial level, an initially set high price without consideration of the sudden increase in demand across Canada significantly reduced coverage and access to an HCV cure. Nevertheless, other factors such as timely access to safe and effective medicines, as mentioned previously in the submission, need to be considered.
- Not only market size but also access to safe and effective treatments in a timely manner is very important. Historically, Canada has benefited from a regulatory and economic environment where drugs are submitted to Health Canada, approved and launched by industry within its first-tier launch countries. Any changes to the PMPRB Regulations, through market size factors or other economic factors must not impact the launch sequence of new drugs or the access to clinical trials as these might negatively affect our current environment. We, as patient organisations, do not want to be relegated to a lower-tier launch country

where we must wait even longer to get access to effective therapies. Looking at the seven new countries proposed for the comparator countries, all have delayed market entry compared to Canada. This is unacceptable to cancer patients and patient groups in Canada. We do not know if this is directly related to market size or not, but clearly they must be removed. Regulatory programmes are already delaying access to drugs in Canada creating potentially negative health outcomes. For example, in oncology, regulatory bodies delayed access to 14 cancer drugs for metastasized solid tumours. Similarly, for mental health medications, including antipsychotics, the average coverage waits for drugs in all public drug plans was 1,173 days, ranging from 290 to 4,146 days, assuming they were listed at all. It is easy to take the logical steps to the resulting detrimental health outcomes to patients requiring access to these medicines. Further delays cannot be permitted to occur.[4]

- It makes sense that cost of drugs be adjusted based on changes in the market size, but these adjustments should also consider the level of innovation and improvement to patient outcomes and savings in other areas of the health care system in addition to other social systems including the criminal justice system, the child welfare system and the disability support system.

III. Gross domestic product in Canada

Consultation Question

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

GDP is a measure of a country's economy. Thankfully Canada's GDP ranks high in the developed world. Hence using GDP seems to be a good measure to be used by PMPRB as it is focussed on our ability to pay. Relative to the 12 comparator countries proposed for comparison in the Regulations, Canada is "in the middle", with 7 countries with lower GDP per capita than Canada.

Recommendation:

1. While we have no objection to Canada considering GDP to determine an excessive ex-factory market entry price, we submit that including other measures such as overall percentage of dollar spent on prescription medicines relative to health outcomes, reduction of hospitalization or other metrics are also relevant and useful. Unfortunately, the issue of silo budgeting, and looking at each piece of the health budget relative to outputs rather than holistically in relationship to their impact on health outcomes, is a serious fundamental flaw with our entire health care system vision and structure.

Consultation Question

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

Recommendations:

1. pCPA should be mandated by the Council of the Federation to negotiate agreements based on such innovative contract approaches as pay for performance, risk sharing agreements

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[4] **"**Economic cost of delayed access to 14 new cancer medicines in Canada's public drug plans", *chp* 2016 May 31, rev.Aug.24, Nigel Rawson, p.9

and other innovative contractual designs, rather than solely on a negotiated price, since that approach will truly reduce prices and the overall drug budget.

2. Government policies should be created that ensure that all savings from drug pricing reductions are returned to the public health budget, or become an automatic rebate to employers in the case of private group insurance plans for use to augment drug coverage for employees with life-threatening or serious illnesses, or become an automatic rebate to individuals with private individual coverage.

Additional comments for consideration:

- Another factor is the fact that Canadians in many disease areas have access to industry-sponsored clinical trials and these are considered important treatment options. If the countries proposed have more limited access to clinical trials, they should be removed.

- Another important factor is the impact that availability and cost of drugs in the health care system can have to drive down costs in other areas of this system. How will these be measured and re-invested under the new regulatory regime?

- One could also argue that economic improvements, because of the increased productivity of employees in the private sector, should be a factor in drug price determination and adjustments. These are not presently being measure and how this would be done remains to be determined.

Proposal #2: Amending the list of countries used for international price comparisons

Consultation Questions

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

It is difficult for the above-signed groups to provide a complete response on what other countries should be included in a new basket of countries without a more fulsome understanding for the rationale for choosing the current 12 countries and the reasoning for excluding other potential candidate countries. We have been told that economic factors, i.e., GDP, and a strong commitment to consumer protection in those countries were primary factors in selecting them. What are these consumer protection mechanisms and how relevant are they to the Canadian system?

Recommendations:

1. During the consultations, we suggested other relevant factors be included. With respect to the proposed list of 12 comparator countries, the federal government should ensure that all factors are considered and compared and that these be made transparent. These include: private/public insurance drug split, health care delivery mix in each country, whether they have a robust Health Technology Assessment (HTA) process, overall health care system structure in each country, demographics of comparator country, price control strategy e.g. free price, maximum price or reimbursement price or a combination of these (we understand that all but Germany have a list price and all but Sweden, Norway and Japan have net prices), price control tools e.g. IRP, TRP, cost per QALY, cost-plus /cost calculation, cost comparison, tendering or pricing negotiations, health systems data collection, monitoring and evaluation, time to market, what drugs are actually covered in those countries and the importance of wide and universal access, access to research and clinical trials and

commitment to innovation and, last but not least, a measure of health outcomes (perhaps those from the WHO) in these countries need to be used in selecting comparator countries.

2. Drugs for life-threatening diseases should receive special attention. The federal government should not use any comparator countries for drugs for life-threatening and serious diseases or conditions in the Regulations that delay market entry longer than Canada's present time to entry as Canadian patients cannot wait any longer than the already lengthy delays experienced to obtain access to badly needed treatments. Thus, some or all the comparator countries should be removed and replaced by more appropriate comparators. The federal government should not use any comparator countries for drugs for life-threatening and serious diseases or conditions in the Regulations that have less clinical trial access in these areas as clinical trials are an important process for access in Canada.

3. The federal government should only select comparator countries that have comparable or better market entry times than Canada and comparable or better access to clinical trials as Canada.

4. All analyses done in support of the Regulations should be made public.

Additional comments for consideration:

- We were advised that some, if not all, of these factors had been considered but were offered no firm assurance that we would have access to these analyses: including private/public insurance drug and health care delivery mix in each country, whether they have a robust HTA process, the entire health care system structure in each country, demographics of the country, price control strategy e.g. free price, maximum price or reimbursement price or a combination of these (we understand that all but Germany have a list price and all but Sweden, Norway and Japan have net prices), price control tools e.g. IRP, TRP, cost per QALY, Cost-plus /cost calculation, cost comparison, tendering or pricing negotiations, time to market, health systems data collection, monitoring and evaluation, time to market entry, what drugs are actually covered in those countries including the importance of wide and universal drug coverage, access to research and clinical trials and commitment to innovation.

- We have reviewed these broader factors in relation to the proposed basket and there are numerous relevant differences between our health care system and aspects of each of these. We will mention a few as examples but there are numerous others that are undoubtedly already part of Health Canada's and PMPRB's analyses of them.

    1. One striking difference is that public spending is by far higher in many of these countries than in Canada e.g. France, Sweden, Norway, United Kingdom, South Korea.

    2. Some of these countries have mandated varying forms of risk sharing agreements with the pharmaceutical industry e.g, Germany, Netherlands, other EU countries.

    3. In Korea, there is no incentive for innovation or the allocation of clinical research, something that is important in our country.

    4. Japan has a system of revising drug pricing downwards for new drugs selling in greater volume than expected and for brand name drugs when generic equivalents hit the market.

5. The point is that each country has an interdependent health care ecosystem and we cannot cherry pick the drug pricing model only, without looking at other relevant aspects of the system to find those that most closely align with our values and our structure. Perhaps this has been done but without seeing the government's analysis, we have no way of determining this.

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

We would submit all the factors set out in in this submission should be considered. For example, comparability of health care systems is important because of the principle of universality; the type of different delivery systems across regions is relevant; reimbursement of drugs either by the public or private systems is also relevant.

Recommendation:

1. Factors that should be taken into account in selecting comparator countries include private/public insurance drug and health care delivery mix in each country, whether they have a robust HTA process, the entire health care system structure in each country, demographics of the country, price control strategy e.g. free price, maximum price or reimbursement price or a combination of these (we understand that all but Germany have a list price and all but Sweden, Norway and Japan have net prices), price control tools e.g. IRP, TRP, cost per QALY, Cost-plus/cost calculation, cost comparison, tendering or pricing negotiations, time to market, health systems data collection, monitoring and evaluation, time-to-market, what drugs are actually covered in those countries and the importance of wide/universal access, access to research and clinical trials and commitment to innovation.

Additional comments for consideration:

- Our health care system is not uniform across provinces, and how it would be standardized, not to the lowest common denominator but to best practices not only within Canada but also in comparison to these countries, must be considered.

- Health outcomes measurements must also be comparison factors, as these play a critical role in determining the value of a drug treatment in any HTA analysis. If PMPRB is to include HTA in its pricing determination, health outcomes must also be included. Additionally, it would be wise to compare health outcomes within the new basket of countries looking for possible correlations between drug expenditures and outcomes as compared to other cost drivers, like hospitalisation, disability. For an excellent discussion of health care based on outcomes, read the World Economic Forum on Africa 2017 Paper[5] and "The Patient Will See You Now", a recent book by Dr. Eric Topol.[6]

- Additionally, health outcome measurements cannot be disassociated from real-world evidence data collection and analysis. It is part of the continuum of health outcomes measurement. Currently the responsibility to oversee, collect, analyse and implement solutions derived from these analyses does not reside with any one government stakeholder e.g. Health Canada, PMPRB, CADTH, pCPA, CAPCA. These agencies as well as registries held by disease groups and health data collection agencies, and the private sector, have a

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[5] https://www.weforum.org/reports/value-in-healthcare-laying-the-foundation-for-health-system-transformation

[6] "The Patient Will See You Now", *Basic Books*, 2015, Eric Topol

stake in real-world evidence generation. It is imperative that there is a common accepted consensus on the definition of real-world evidence, how to collect and analyze it and the purposes for which it will be used.

- Cultural factors should be considered when comparing Canada to other countries. It is important that we, as a culturally diverse country, find our own comfort levels in making value judgments about what we are willing to pay for the value we are seeking in exchange for better health outcomes.

- Lastly, the issue of how we see our role as a world leader in subsidizing prices and access to necessary medicines in the developing world has not been addressed at all. This was a question often asked when combination therapies were developed for HIV that were out of the reach of people in developing countries. Cancer is arguably comparable.

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

Until we can do a more in-depth analysis of comparator countries and the factors they bring to the comparator basket, we cannot provide comprehensive comments on this question. We reserve further comments until more information becomes available to us from various sources.

We also request that more details be provided on market entry for new products in the new basket countries, as this will undoubtedly influence how new drugs will be introduced in Canada, which could result in longer wait times for patients to gain access to these drugs.

When examining the OECD countries chosen as the new basket of 12 comparator countries, it seems that the average price ratio from these countries are at, or close to, the median OECD price ratio. This begs the question: why not just use this median price ratio as one of the factors going forward? In the document provided the number for this median is about 22 per cent below that of Canada. Why do the proposed guideline changes not acknowledge this?

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

Consultation Question

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

This seems like a reasonable approach and a way to be more efficient with the resources at the disposal of the PMPRB. Clarification that the complaints process can be made by anyone should be added.

Recommendation:

1. There should be a clarification added to the proposed patented generic drug process explaining that the complaints process can be accessed by anyone.

Proposal #4: Modernizing reporting requirements for patentees

Consultation Questions

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

2. Is this information generally available to patentees?

This question is directly related to Question #1. See our comments under that section.

Proposal #5: Providing information related to third party rebates

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

First, the question is not clear and needs to be revised since the definition of "indirect" discounts and rebates is not defined. We were told that it referred to rebates to pCPA, private payers and cards provided to individual payers by companies to cover deductibles and prescribing fees. If so, this should be made clear.

It should also be clearly stated how this information will be used. Unless there is a purpose for it, there is no point asking patentees to do more work than required.

Recommendation:

1. The definition of "indirect" discounts and rebates should be defined in the Regulation. The Regulation should clearly state how the information about indirect discounts and rebates will be used.

Additional Comments and Recommendations:

Patient values are not discussed to any extent in the consultation document. We find this antithetical to the goals of increasing affordability for medicines to Canadians and to the stated aims of all Canadian governments to ensure patient-centred care in this country.

Recommendation:

1. Patient values must be added in the Regulation as an equally important factor for the PMPRB to consider as any others when determining whether a drug price is excessive since all Canadian governments have expressed that their health policies are based on patient-centred care.

2. PMPRB and Health Canada should develop a rigorous monitoring and evaluation framework for the federal regulation of drug pricing designed with patient groups and reviewed annually and modified as required.

Other recommendations for consideration:

1. An efficient, effective and mandatory dispute resolution mechanism within PMPRB for excessive pricing in the breakthrough drug category should be created within PMPRB such as a mandatory Alternative Dispute Resolution process with publicly published reasons for the decision as well as regular re-evaluation of a well-defined class of breakthrough drugs. This will address the core affordability problems of PMPRB.

2. The *Patent Act* should be amended to delete the Consumer Price Index (CPI) as an automatic increase mechanism for therapies.

4. Conclusions

In every pricing review, there is always room to reduce drug costs through negotiation but, if the impact of lowering the drug entry price in Canada by 20 per cent or more is less or delayed access to treatments for patients, patients and their organizational representatives will not support it.

Our stated concerns about the basket of countries leading to increased delays in access is not without an evidentiary basis. We have done an analysis of launch times and drug prices in several countries, and there appears to be a direct relationship. For instance, Switzerland launches new medicines 142 days after market access while Canada launches such products 357 days after market authorization. Launch times in Germany and the UK were on average within 4 to 6 months while France, Spain and Italy took more than a year.

As the federal government looks at drug pricing policy changes, they should do so in the context of overall health outcomes, the impact on the entire health care system and employers. The real issue for many people in Canada is lack of access or inadequate access to necessary medicines. This is a problem worth solving. The main problem for the poor is the lack of funds to buy drugs or the inability to pay the deductibles, co-pays and other costs associated with being uninsured or underinsured. The federal government should set up a fund that these people can access across Canada to deal with this inequity in access.

Final recommendation:

1. The federal government must ensure that there are no unintended and unforeseen adverse consequences to public payers of a lower entry price into Canada for public and private payers by reducing the overall amount available to provincial/territorial payers for price negotiations before promulgating these Regulations. Such an adverse impact will mean less access to necessary medicines for eligible people in Canada and this is surely not the intention of the federal government.

The federal government must show leadership in health by convening a multi-stakeholder group including meaningful patient group representation to find a common vision for the health care system founded on value-based health outcomes and to determine how to collaborate to achieve that goal together.