



February 13, 2020

Patented Medicine Prices Review Board
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Submitted via email: PMPRB.Consultations.CEPMB@pmprb-cepmb.gc.ca

Re: Input to Proposed Changes to the PMPRB Draft Guidelines

Dear Sir/Madam,

Thank you for the opportunity to submit comments on PMPRB's Draft 2019 Guidelines that is intended to determine if a patented medicine is priced excessively in any market within Canada.

With these new guidelines, PMPRB proposes to streamline its basket of comparator countries and to include additional section 85(1) factors for the determination of the Maximum Rebated Price (MRP) for Category 1 drugs. This include pharmacoeconomic value derived from health technology assessments conducted by CADTH and/or INESSS (Quebec) for drugs where annual regimen cost is greater than 50% of GDP per capita (2018 GDP per capita stands at US\$44,200 or C\$57,800). Further, the MRP will be set at a 50% markup to its PEP or pharmacoeconomic price for low prevalence drugs. MRP will be assessed against net price (list price less of any rebates) and there is a \$25M threshold for market size before the PEP price undergoes price adjustments.

Here are responses to some of these key changes.

Inclusion of New Factors

PMPRB has proposed to add pharmacoeconomic value (as measured by incremental cost per QALY ratio) as one of the new factors to subsection 85(1); the other factors being market size and GDP and

GDP per capita. With the addition of these new factors, PMPRB clearly intends to move towards a value assessment framework in its ceiling price determination with the use of a value-based price or pharmacoeconomic price (PEP). This is the price where the cost-effectiveness ratio is equal to an arbitrary set threshold value of \$60,000/QALY. There is no intention currently to adjust this value by other key factors that are not yet considered including the absence of any other therapies (unmet clinical need), the severity of the illness, reward for risk-taking, innovation, patient values, societal values, end-of-life adjustments and other policy and economic factors.

Similar forms of value-based pricing have been attempted by other jurisdictions (notably UK's NICE) and in all effects have been put on hold or abandoned due to the complexity of defining value or adjusting a threshold-based price for other key value factors. These attempts did however introduce risk sharing agreements with manufacturers with longer-term evidence development arrangements and enabled additional dimensions to be considered when considering value-for-money for public reimbursement of drugs (such as innovation and end of life adjustment). The point is these negotiated schemes are necessary to extract dynamic and static efficiencies rather than regulated schemes. As such, it is important to have a deliberative decision-making process to arrive at value-for-money decisions that enable affordability to the public payers, enable early access to newer highly-effective drugs and disincentive unreasonable price setting by manufacturers for drugs that do not show sufficient magnitude in clinical and safety benefits compared to existing therapies or biologics. (Biologics effectively remaining a monopoly even after patent expiry due to high entry barriers for biosimilars). Negotiated agreements also enables flexibility in pricing when the drug shows minimal added benefit for a newer indication thereby enabling prices to match to the value of the drug.

PMPRB's attempt to derive value-based price by simply using and adjusting the PEP price seems simplistic and inaccurate. The derivation of PEP using point estimates from a pharmacoeconomic model that itself can have high degrees of uncertainty is therefore flawed. This is especially critical since the PEP is being used to set the MRP in a regulatory setting where PMPRB has the power to

impose strict remedies that include paying the government the excess revenue if they deemed that the drug price is excessive. In addition, PMPRB can issue notices for excessive price hearings and the failure to comply with providing information to PMPRB can result in summary conviction, fines or imprisonment (subsection 76.1(1) of the Act).

Use of supply-side threshold

PMRPR noted that the threshold value of \$60,000/QALY was based on final report commissioned by PMRPRB (Working Group to Inform PMPRB Steering Committee on Modernization of Price Review Process Guidelines) as well as published work that estimated supply-side thresholds from the UK, Spain and Australia. PMPRB's use of \$60,000/QALY is not a reasonable value for setting the Pharmacoeconomic Value Threshold (PVT) for these reasons:

First, the Working Group has noted that no HTA agency has set an explicit supply-side threshold that is empirically derived for Canada using appropriate methodologies. Current thresholds based on past decisions made by these HTA agencies (CADTH and/or INESSS) show thresholds that range from \$100K/QALY for non-oncology therapies to higher thresholds for oncology drugs. PMPRB's threshold of \$60K/QALY fall well short below these thresholds that are regularly applied in CADTH/pCODR and INESSS deliberations in its recommendations for public reimbursement of drugs.

In addition, PMPRP refers to studies that attempted to derive a supply-side threshold for Canada. The working group has only identified one study (Ochelek, 2018) which estimated \$30K/QALY. However, there are major limitations to this study including the methodology (use and choice of instrumental variables) that is inappropriate for a study of this nature as well as using UK source for some of its cost data. Reference was also made to similar studies done in the UK which indicated a threshold of £12,935/QALY which is substantially below what NICE (the HTA agency in UK) actually used to determine cost-effectiveness for medicines that likely will be grouped as Category I.

The threshold also seems to fall well below those determined by other work such as the \$150,000K in the US (ICER), WHO recommendation of up to 3X per capita GDP and the UK Department of Treasury which recommended 2X the per capita GDP.

PMPRB currently relies on supply-side or opportunity cost theoretical conceptual approach to determine its threshold. There are however, demand-side or willingness to pay thresholds that PMPRB has to consider too. This necessitates relying on measures such as surveys of willingness to pay or from revealed choices. CEA thresholds and the use of cost-effectiveness analysis itself based on the current conceptual framework can create large degrees of uncertainty in ceiling price determination. Alternative conceptual models (e.g. based on risk aversion) may need to be considered rather than awaiting improvements in methodology that use the current conceptual model for deriving supply-side thresholds. As of now, no study of this nature has been conducted in Canada using Canadian costs with an appropriate methodology. Any effort to undertake this will take years to do especially for the study to be published in peer-reviewed journal. With no sound threshold to base its value-based price, it is premature for PMPRB to include pharmacoeconomic factor in its MRP setting.

Alternative Methods

The use of CEA and the issues around the interpretation and determination of thresholds is part of the reason why some countries do not set prices based on CEA but instead focus on the determination of added therapeutic benefit. For example, Germany (which is one of the PMPRB11 countries), defines the degree of clinical benefit into six major groups – major, considerable, minor, non-quantifiable, none or less. Reference pricing is used only when no major benefit is found with respect to current therapies that are already available or used in any adapted form. The price of the new therapy is then set by the lowest priced competitor.

Perspective

PMPRB proposes using the perspective of Canada's publicly funded healthcare system. Hence the threshold that it proposes is implicitly tied to fixed budgets in a publicly reimbursed system. PMPRB

however is using this threshold also for patented drugs that are privately covered and not publicly reimbursed. Since PMPRB's MRP covers all Category 1 patented medicine, the PEP derived from this perspective might potentially hold for publicly reimbursed drugs (though as noted earlier, there are major shortcomings using the proposed threshold), but it may not hold for those that are only available in the private insurance market or paid directly from out of pocket by patients.

In addition, PMPRB's use of other sources as rationale for setting its \$60,000/QALY threshold was based on analysis from the UK, Spain and Australia, which are all based on publicly reimbursed health systems where there are no legislations setting ceiling price that is applicable to all patented medicines either publicly or privately reimbursed.

Use of QALYs

The use of quality-adjusted life years (QALYs) has benefited drugs that treat serious illnesses or disabilities. However, it can be viewed as undervaluing treatments for population groups where therapies prolong life without major improvements in quality of life. Treatments for patients with serious disabilities or illness have the ability to show more QALYs gained and therefore and command a higher cap. As such, PMPRB's sole use of QALYs as the one and only measure of health gain can undermine its ability to be transparent and fair to all patient population when it comes to the setting of ceiling price.

Reference Case

Neither CADTH nor INESSS create their own cost-effectiveness (CEA) models but instead reviews CEA models that are submitted by manufacturers. The models are then modified through changes in assumptions to arrive at an adapted model with a cost-effectiveness ratio that is often higher than the one submitted by manufacturers. The adapted CEA model is often not shared with the manufacturer nor is it sent for out for peer review. In addition, there is no prior discussion on these adaptations to ensure that they are reasonable and results in less uncertainty in the parameters. In some cases, there can be inconsistencies and inaccuracies in the assumptions used by HTA agencies in adapting these

models to arrive at a cost/QALY. Further, CADTH and INESSS can arrive at different recommendations using the same manufacturer submitted models.

The mandate of HTAs is to provide recommendations to governments on public reimbursement. Specifically, CADTH was set up to provide ‘Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs and medical devices in our health care system’. As part of this mandate, CADTH requests and reviews these CEA models to determine value-for-money and make recommendations on whether further negotiations need to be undertaken between the provinces (which hold the budget as CADTH does not hold any drug budget) and the manufacturer before the drug is listed for public reimbursement. The mandate of CADTH was not to set a pharmacoeconomic price that will be used by a regulatory body such as PMPRB to set the price. Given the large uncertainty that is inherent in these models, use a point estimate from the CADTH model is inaccurate for setting the PEP.

If PMPRB still wants to include pharmacoeconomics as one of the factors, it may want to be more involved or act as active observers in the deliberative process by these HTA organizations. This will provide greater context in the interpretation of the final recommendations made by these HTA agencies including the dealing of uncertainty especially relating to projections around long-term survival and outcomes. In addition, it will enable PMPRB to see how analysis of efficacy and safety data from the pivotal trials are determined and how it can differ from the one conducted by PMPRB’s own scientific committee (Human Drug Advisory Panel) as well as from Health Canada.

Determining caps for transformative therapies

PMPRB noted as rationale for making amendments to the Patented Medicines Regulations, there is a shift in the industry’s R&D from low-priced, small molecule drugs towards high-priced biologics that target small patient populations. One emerging area is the rise of high-impact transformative therapies that are administered one-time or for a very short time. This includes revolutionary and very effective cell and gene-based therapies including chimeric antigen receptor therapies where cells are

taken from a patient's blood and then genetically modified before being infused back into the patient. The cost for these one-time therapies can rise to the millions. In December 2019, Ontario announced it will cover the cost of Kymriah for eligible patients (Quebec being the first province to cover this CAR-T therapy). The therapy has been approved by Health Canada to treat two life-threatening blood cancers: acute lymphoblastic leukemia (or ALL) in children, and a form of non-Hodgkin's lymphoma in adults.

Though preliminary CEA analysis show that these treatments can be cost-effective, determining a cap for these treatments can be challenging with limited external reference pricing and payment schemes that can be structured to be paid off over several years. It has been proposed that for this one-time administration for these therapies specifically for ultrarare diseases, the threshold should be much higher. In the US, the Institute for Clinical and Economic Review has described a range that can go up to C\$650,000/QALY for diseases that are ultrarare. In the UK, NICE (National Institute for Health and Care Excellence) had described a variable threshold whose upper bound can rise to C\$500,000/QALY.

In addition, these treatments may not be technically considered drugs as they are not manufactured in traditional ways of small and big molecule drugs and hence may fall outside of PMPRB's mandate.

Indication-based Pricing

PMPRB noted that it only sets a single price ceiling for drugs with multiple indications. However, these does not align with the value-based pricing that PMPRB is seeking to move towards with the inclusion of pharmacoeconomic value test. With the increasing number of indications available for one patented drug, each with varying degrees of efficacy and therapeutic value for its small patient population, indication-based pricing may represent the best way forward to ensure that prices reflect the value to the patient. Further, with many disease states increasingly being sub-divided into smaller categories to procure rare disease designations, varying degree of therapeutic value can be found for

each of these diseases. Indication-based pricing enables prices to match the therapeutic value for the patient.

Regional Differences

With different health care systems including different skill levels of healthcare practitioners and varying quality of healthcare faced by clinical trial participants around the globe, the clinical efficacy of drugs can vary by regions/countries (e.g. North America vs Asia-Pacific). PMPRB may therefore be interested to additionally consider subset of results from registration trials that are similar to Canada (e.g. North American trial participants) in its derivation of MRP.

Conclusion

Given the serious limitations proposed in its determination of PEP, it is recommended that PMPRB remove or delay pharmacoeconomic factor in its Section 8 factors. Since PMPRB is a regulatory agency with ability to impose financial penalties on industry, it becomes important to ensure that any determination of PEP or value-based pricing is done accurately. If the intention is to try to ensure that medicines are not excessively priced, then it becomes necessary to ensure that prices reflect the value of the drug. A better way therefore to do this it to investigate indication-based or target-based pricing and figure out how to implement it especially for Category I drugs become more personalized and target patients based on biomarkers.

I hope these comments will be useful to PMPRB as it continues to finalize its guidelines based on these consultations.

Sincerely,

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Mayvis Rebeira, PhD

Research Fellow

References

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