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February 14, 2020

Dr. Mitchell Levine, M.D., M.Sc., FRCPC, FACP, FISPE
Chair, Patented Medicine Prices Review Board
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Ottawa, Ontario K1P 1C1

Dear Dr. Levine:

Subject: Patented Medicine Prices Review Board (PMPRB) Guidelines

On behalf of EMD Serono Canada ("EMD Serono"), I am writing to provide input to the Consultation on the proposed 2019 PMPRB Draft Guidelines (the "Draft Guidelines").

EMD Serono, the Canadian biopharmaceutical business of Merck KGaA, Darmstadt, Germany, is committed to ensuring patients in Canada will benefit from innovative products in oncology, neurology, fertility and endocrinology. Our pipeline includes investigative therapies in neurology, oncology and immuno-oncology. In Canada, we support research through clinical trials in multiple sclerosis (MS) and oncology. EMD Serono has more than 100 employees across Canada with its headquarters located in Mississauga, Ontario.

EMD Serono is a member of Innovative Medicines Canada (IMC) and fully supports the submission from our industry association. In this letter, I will articulate our concerns about the new approaches to regulate the prices of patented medicines specified in the Draft Guidelines.

Our key concerns are outlined as follows:

1. The lack of information to evaluate the impact of the Draft Guidelines creates pricing uncertainty for manufacturers;
2. The Draft Guidelines fail to recognize the clinical benefit of new medicines and introduce a new test that may benchmark prices of generic products in reference markets;
3. The new pharmacoeconomic factors are subjective and introduce substantial uncertainty;
4. Confidential prices can be reverse engineered to reveal negotiated net prices; and
5. The belief that the Draft Guidelines will not delay or reduce access to new medicines is deeply flawed.

I expand on our concerns below. Furthermore, the unintended consequences of the Draft Guidelines are illustrated through a case study of an innovative medicine we recently launched in Canada.

At EMD Serono, our mission is to create, improve, and prolong the lives of patients. The Draft Guidelines include new measures in the framework to establish prices that are unprecedented on a global scale; these new factors introduce uncertainty and devalue significant medical innovations that are designed to advance the health of Canadians. The Draft Guidelines put patient access to such innovations at risk.

As such, we respectfully urge the Government and the PMPRB to delay implementation of the Draft Guidelines until comprehensive analysis of the impacts can be appropriately modelled, published, and transparently discussed with stakeholders.

1. *The lack of information to evaluate the impact of the Draft Guidelines creates pricing uncertainty for manufacturers*

In December 2018[1] and December 2019[2], the PMPRB published case studies designed to illustrate how the new regulations will be applied. However, the case studies provided by the PMPRB did not include sufficient information to validate or model the broader impact of the new price regulations.[3] Published independent work demonstrates that the new pricing rules will require manufacturers of innovative medicines to lower prices for some products by as much as 70-90% to establish an acceptable price in Canada.[4] This reduction in potential price will make it challenging, and in some cases impossible, for companies to launch new therapies in Canada.

2. *The Draft Guidelines fail to recognize the clinical benefit of new medicines and introduce new tests that benchmark prices of generics in reference markets*

The existing PMPRB Guidelines evaluate the therapeutic benefit of patented medicines. Under the current regime, new medicines that improve clinical benefit over existing therapies are rewarded through the application of different tests that allow manufacturers to obtain higher prices. These prices reflect the additional value and therapeutic benefit to patients and the healthcare system.

In contrast, the Draft Guidelines no longer recognize the therapeutic benefit of a medicine. Instead, the Draft Guidelines incorporate new median Therapeutic Class Comparison (TCC) tests which will include the prices of patented and non-patented medicines and establish the median price of those products.

The broad inclusion of the median TCC test in the Draft Guidelines, irrespective of a medicine's therapeutic benefit, is concerning. In effect, new therapies that substantially improve clinical outcomes, even if they are priced lower than existing, non-excessively priced alternatives, could still be deemed to have an excessive price under the Draft Guidelines. This approach penalizes new medicines and is a disincentive for manufacturers to bring forward new innovations. Furthermore, the Draft Guidelines raise the possibility that the Maximum Rebated Price (MRP) will be set by a new international TCC (iTCC). The Draft Guidelines open the possibility that the iTCC test will benchmark the prices of patented innovative medicines in Canada to the level of generic medicines in reference countries.

The introduction and application of a new price test that benchmarks new medicines to the price of generics in reference markets is not commercially viable in Canada and penalizes manufacturers of innovative medicines. As such, the Draft Guidelines will effectively inhibit the commercialization of patented medicines in Canada. Most importantly, the approach outlined in the Draft Guidelines will reduce patient access to innovative products.

3. *The new pharmacoeconomic factors are subjective and introduce substantial uncertainty*

For some patented medicines, the Draft Guidelines specify the use of a pharmacoeconomic formula to determine non-excessive prices. This approach is worrisome, as the use of incremental cost per quality-

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[1] PMPRB. Guideline modernization: case studies, January 8, 2019. http://www.pmprb-cepmb.gc.ca/view.asp?ccid=1419&lang=en.
[2] PMPRB draft guidelines consultation, December 10, 2019 (slides 31 and 32). https://www.canada.ca/content/dam/pmprb-cepmb/documents/consultations/draft-guidelines/presentation-dec10-en.pdf.
[3] PMPRB draft guidelines consultation, December 10, 2019. https://www.canada.ca/content/dam/pmprb-cepmb/documents/consultations/draft-guidelines/presentation-dec10-en.pdf.
[4] Rawson NSB, Lawrence D. New patented medicines regulations in Canada: updated case study of a manufacturer's decision-making about regulatory submission for a rare disorder treatment. *Can Health Policy*. Toronto: Canadian Health Policy Institute, 2020. https://www.canadianhealthpolicy.com/products/new-patented-medicine-regulations-in-canada--updated-case-study---en-fr-.html

adjusted life year (QALY) to set prices is fundamentally inappropriate. Pharmacoeconomics and cost per QALY may help inform reimbursement decisions, and even there, the applicability is limited by model uncertainty.

Cost per QALY calculations condense complex patient and caregiver experiences into a point estimate, which inherently has significant variation and uncertainty. QALY assessments as used by health technology assessment (HTA) agencies CADTH and INESSS fail to account for important components of value, such as indirect economic impacts that are relevant to public payers. Cost per QALY estimates are not objective and are dependent on the assumptions and time horizons used; neither of these factors have a common international, let alone Canadian, standard. Furthermore, pharmacoeconomic evaluations by HTA agencies have substantial limitations, including the facts that they are subjective, variable and not peer reviewed. Consistent with this, the Consultation Backgrounder from the PMPRB itself notes that empirical work on a supply-side cost effectiveness threshold in Canada is in a "relatively embryonic state."[5]

The Draft Guidelines propose to use cost per QALY thresholds to determine the willingness and ability to pay for every payer and individual in Canada. This approach is unprecedented globally in terms of price regulation for innovative medicines. Importantly, cost per QALY thresholds are not broadly or consistently considered in the HTA process. Where they are considered, they are only one factor to help inform evaluations and reimbursement decisions. To our knowledge, cost per QALY thresholds have never been employed by a national price regulator to set the maximum price of innovative medicines for an entire country. Furthermore, the planned threshold of $60,000 per QALY specified in the Draft Guidelines will put Canada behind global jurisdictions that place a higher value on access to innovative drugs.

4. Confidential prices can be reverse engineered to reveal negotiated net prices

The Regulations require manufacturers to report confidential benefits and rebates negotiated with third parties. Such negotiated agreements have helped improve patient access to medicines; increased the ability of smaller provinces and payers to fund medicines; and improved formulary consistency across public payers in Canada. The ability to negotiate confidential rebates allows various factors to be taken into consideration without having to resort to a 'race to the bottom' on rebates. The reliance on calculating rebated prices in the Draft Guidelines increases uncertainty for manufacturers that develop innovative medicines.

The success of such negotiated agreements depends on the ability for the terms to be kept confidential in the context of global price referencing and market competition within therapeutic classes. The obligatory reporting of net benefits would have the effect of making the PMPRB a party to these agreements and commercial benefits, in part because the PMPRB intends to use that information to secure lower "non-excessive" prices.[6]

The Draft Guidelines specify that the Pharmacoeconomic Price (PEP) evaluation of patented medicines will be published. With a published PEP, other countries or parties will be able to back-calculate and identify the rebated price in Canada. This knowledge will have global ramifications that impact manufacturers' operations in other countries. More importantly and of greater concern for Canadians, these policy changes and uncertainties may lead to companies avoiding the above situation by simply

[5] Consultation Backgrounder, November 2019, p. 7. https://www.canada.ca/content/dam/pmprb-cepmb/documents/consultations/draft-guidelines/backgrounder-draft-guidelines-en.pdf.
[6] PMPRB guidelines scoping paper – high level overview of potential new framework. (Canada Gazette, Part I), December 18, 2017, http://www.pmprb-cepmb.gc.ca/view.asp?ccid=1341.

not launching innovative products in Canada. This would clearly have a negative impact on patient access to new medicines.

5. The belief that the Draft Guidelines will not delay or reduce access to new medicines is deeply flawed

The view that lower drug prices in Canada will not negatively impact the availability of new innovative drugs is deeply flawed. The approach outlined in the Draft Guidelines will prevent or delay the introduction of new innovative treatments in Canada. The unintended consequence is the Draft Guidelines will have a significant impact on patients who are desperate for innovative treatments to treat their conditions.

Indeed, a 2017 survey of multi-national pharmaceutical executives in 31 markets drew attention to the fact that stiff price cuts levied against innovative drugs hamper a country's ability to secure and sustain investment, and in particular noted that this should be a "red flag" to economies considering a similar approach "such as Canada in its proposed amendments" to the PMPRB.[7]

More recently, a report of a survey of global and Canadian pharmaceutical executives performed for Life Sciences Ontario about the new pricing regulations reported that **all** respondents thought that the changes would negatively affect their overall business plans in Canada and almost all responded that they would adversely impact product launches, commercialization and supply of current products (97%), employment in Canada (97%) and clinical research in Canada (91%).[8] This research clearly demonstrates the negative impact of the Draft Guidelines on industry and commercialization of patented medicines in Canada.

The unintended consequences of the Draft Guidelines are demonstrated through a case study

An innovative, patented medicine recently launched by EMD Serono illustrates the impact of the Draft Guidelines. In 2018, the CADTH pan-Canadian Oncology Drug Review (pCODR) evaluated our immuno-oncology product [Pr]BAVENCIO® (avelumab for injection) for use in previously treated adults with metastatic Merkel Cell Carcinoma (mMCC). mMCC is a rare, aggressive skin cancer with high unmet medical need. In its recommendation that BAVENCIO be funded by public drug plans, pCODR noted:[9]

> "Metastatic Merkel Cell Carcinoma (mMCC) is an aggressive, uncommon skin cancer that is increasing in incidence. […] Although chemotherapy represents the current therapy option, there is no standard of care for the treatment of mMCC in previously treated adults. […] pERC concluded that there is a substantial unmet need for alternative options with fewer and more manageable adverse effects than chemotherapy, to reduce disease burden, and prolong survival."

Based on the current PMPRB Guidelines, the list price of BAVENCIO is "Within Guidelines" and is therefore non-excessive. The list price of BAVENCIO is also below the current median of the new PMPRB11 reference basket and is therefore expected to remain "Within Guidelines" after the PMPRB

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[7] Ascending to the peak of biopharmaceutical innovation: Biopharmaceutical Competitiveness and Investment Survey, 4th Edition. Washington, DC: Pugatch Consilium, 2017. https://www.pugatch-consilium.com/reports/BCI_2017_Report.pdf.
[8] Impact of PMPRB pricing changes: final research report. Toronto: Life Sciences Ontario, 2020. https://lifesciencesontario.ca/wp-content/uploads/2020/02/Research-Etc.-PMPRB-Survey-02-03-20.pdf
[9] CADTH pCODR pERC recommendation for BAVENCIO, March 2018. https://www.cadth.ca/sites/default/files/pcodr/pcodr_avelumab_bavencio_mcc_fn_rec.pdf

implements the Draft Guidelines.

However, BAVENCIO represents an important case study regarding the application of new price evaluation factors. Below, we model a scenario where BAVENCIO is launched in Canada after implementation of the Draft Guidelines (i.e., a non-grandfathered medicine); in this scenario the PEP and $60,000 per QALY rules would apply.

The Draft Guidelines state that the PEP is based on the incremental cost-effectiveness ratio (ICER) derived from the pharmacoeconomic evaluation by the HTAs. First, the pCODR Final Economic Guidance Report for BAVENCIO includes two different pharmacoeconomic scenarios and ICERs:[10] versus best supportive care, with an ICER range of $119,845 to $126,533 per QALY; and versus chemotherapy, with an ICER range of $84,155 to $97,962 per QALY. Furthermore, INESSS generated different pharmacoeconomic outputs due to differences in their model. The range of ICERs necessarily means there would also be a range of PEPs calculated by the PMPRB.

Which HTA review and pharmacoeconomic scenario would be applied to calculate a PEP consistent with the $60,000 per QALY rule? The Guidelines are unclear on how the PEP will be calculated in practice and offer no real-world examples. This introduces significant uncertainty for manufacturers to evaluate the commercial potential of an innovative medicine in Canada.

Furthermore, the Draft Guidelines include the calculation of a market size impact for new medicines and specify a threshold of $25 million in revenue. BAVENCIO was first developed for the treatment of previously treated adults with mMCC, an aggressive cancer that affects a relatively small population; revenue based on this population would not trigger the market size reduction. However, BAVENCIO is also being developed as an investigational treatment for other oncology indications with larger patient populations. In the scenario where BAVENCIO is launched after implementation of the Draft Guidelines, the addition of new indications and larger populations would increase revenue above the $25m threshold and trigger reductions based on market size. These new market size factors would create further uncertainty in the final price and commercial potential of BAVENCIO. The market-size adjustment threshold is a disincentive to develop innovative medicines that treat larger numbers of patients in Canada, or to expand the clinical benefit for those medicines to other patient populations.

The above case study demonstrates the significant pricing uncertainty going forward due to the Draft Guidelines. Substantial costs are incurred to launch a new medicine in Canada, including regulatory approvals, reimbursement submissions, payer negotiations and medical, sales, legal and distribution costs. Broadening a medicine's indication that increases revenue past the $25 million threshold, thereby triggering revenue reductions as specified by the Draft Guidelines, would require broader considerations about the requisite investments and whether a commercial launch in Canada is viable.

These new factors will have unintended consequences. The Draft Guidelines will significantly lower price potential in Canada compared to other countries, including the new PMPRB11 reference basket. In simple terms, product launches may be delayed in Canada due to the potential impact on pricing in other countries. Furthermore, new economic factors and adjustments based on market size make Canada a less favourable environment to launch products due to the inherent uncertainty of how these factors will impact revenue. Finally, lower prices and revenue may compromise the development by manufacturers of robust support programs that benefit patients and the health care system. Quite

[10] CADTH pCODR Final Economic Guidance Report for BAVENCIO, March 2018. https://www.cadth.ca/sites/default/files/pcodr/pcodr_avelumab_bavencio_mcc_fn_egr.pdf

simply, the Draft Guidelines make Canada a less attractive market for both launch and investment. The loss of attractiveness will reduce patient access to new medicines in Canada.

Conclusion

The role of the PMPRB is to protect Canadian consumers by ensuring the prices of patented medicines sold in Canada are not excessive. The PMPRB should limit its role to establish reasonable ceiling prices. From there the pan-Canadian Pharmaceutical Alliance (pCPA), provinces and other payers can continue to negotiate appropriate terms with pharmaceutical manufacturers. This system allows payers to rely on HTA and market size metrics to inform their reimbursement decisions and provide patient access to new medicines.

If the Draft Guidelines are implemented in their current state, EMD Serono will be severely challenged to launch products in Canada on a priority basis. This will negatively impact patient access to innovative medicines.

Our ask is simple: We strongly yet respectfully urge the Government and the PMPRB to delay implementation of the Draft Guidelines. A comprehensive analysis of the impact of the Draft Guidelines should be conducted, published, and transparently reviewed and discussed through meaningful consultation with stakeholders. We envision a prudent, more collaborative consultation based on constructive dialogue from stakeholders that is incorporated by the PMPRB. This approach will help mitigate the issues and unintended consequences identified by us above, by IMC, by patient groups and other stakeholders.

An appropriate balance is required between improving the affordability of medicines, ensuring timely patient access to medicines, and creating a world-class innovative life sciences ecosystem. The implementation of the PMPRB regulations and Draft Guidelines will have the opposite effect.

Sincerely,

Gaby Murphy
Managing Director

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