RAREi
THE CANADIAN FORUM FOR
RARE DISEASE INNOVATORS

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Dr. Mitch Levine
Chair, Patented Medicine Prices Review Board
333 Laurier Street, Suite 1400
Ottawa, ON K1P 1C1

Subject: Input on Draft Patented Medicine Prices Review Board (PMPRB) Guidelines

Dear Dr. Levine:

On behalf of the Canadian Forum for Rare Disease Innovators (RAREi), we want to thank you for the opportunity to provide our feedback on the PMPRB's draft guidelines. We also want to recognize and thank the PMPRB staff for the opportunity to meet with Executive Director Doug Clark and other colleagues on January 10, 2020.

RAREi is a group of eleven small to medium-sized global biopharmaceutical companies[1] focused on researching, developing, and commercializing treatments for rare diseases.

While we support the federal government's objectives of improving access and affordability of medicines, RAREi does not believe the proposed regulations will achieve these health care system objectives. In fact, since our inception in 2018, we have been expressing our serious concerns with regard to the federal drug pricing controls as they are proposed.

We were therefore disappointed to see that the changes made to the *Patented Medicines Regulations* in August 2019 did not reflect the input received despite significant concerns raised by RAREi and dozens of other health system stakeholders and key provinces.[2] In addition, we believe that, the way in which the PMPRB is now proposing to implement the regulatory changes via its draft guidelines is not a viable approach. It will create an unworkable and unpredictable system that requires prices to be reduced to unreasonably low levels, which will limit access to rare diseases medicines for Canadian patients. This will substantially reduce Canada's attractiveness as a market for commercializing rare disease treatments and conducting clinical trials. The end result will be that patients affected by rare disorders in Canada will be harmed, as many of them rely on new therapies to get better and even survive.

The new regulations and the guidelines are not consistent with the federal government's recent efforts to enhance access to rare disease treatments via its Budget 2019 commitment to develop a national rare disease strategy supported by investments of $500 million annually starting in 2022-23. A rare disease strategy, as well as a national pharmacare program, will not benefit patients if new treatments

[1] Alexion Pharma Canada Corp., Amicus Therapeutics, Inc., Biogen Canada Inc., Biomarin Pharmaceutical Inc., Horizon Therapeutics Canada, Ipsen Biopharmaceuticals Canada Inc., Mitsubishi Tanabe Pharma Canada Inc., Recordati Rare Diseases Canada Inc., Sobi Canada, Ultragenyx Canada Inc. and Vertex Pharmaceuticals (Canada) Inc.

[2] PDCI sharing site: http://www.pdci.ca/sharing-responses/

are not available or are only made available at a much later time in Canada versus other countries with comparable health care systems as a result of the new federal price controls. The new pricing rules are also at odds with provincial efforts in improving access to rare disease medicines, such as the approach being developed by the Expensive Drugs for Rare Diseases Working Group, Quebec's new paradigm for evaluating rare disease treatments and its anticipated rare disease strategy and Ontario's interest in focusing national pharmacare discussions on finding a solution for rare disease medicines.

Ideally, RAREi would like to see the regulations changed to remove, at minimum, the untested and uncertain economic factors. Current population-based pharmacoeconomic (PE) methodologies and analyses tend to reflect a certain bias against rare and ultra-rare treatments. As such, the current guidelines would move in the wrong direction by entrenching flawed PE analyses as part of a national pricing regulation system. This approach has not been attempted by any other country and should not be pursued here.

We believe the discussions on national pharmacare and a national rare disease strategy represent a unique opportunity for the federal government to work with the provinces and territories to address outstanding gaps and challenges relating to the reimbursement of rare disease medicines. In particular, this dialogue provides the opportunity to develop a new approach to managing rare disease treatments and achieve savings through negotiations rather than through rigid regulations.

That said, we want to positively contribute to the guidelines consultations in order to help minimize the negative impact the new pricing system will have on patient access to medicines and clinical trials. In this context, we have developed the attached submission, which focuses on elements of the guidelines that are of particular concern for the commercialization of rare disease treatments. Please note that RAREi's feedback is intended to complement the input provided by Innovative Medicines Canada and BIOTECanada.

Given the challenges outlined in our submission, we recommend, at minimum, that the PMPRB:

- **Hold back on implementing the new economic factors** until their impact on rare disease treatments and clinical trials have been appropriately assessed and that this data has been shared with the industry and other health system stakeholders.
- **Create a technical working group focused on rare disease treatments** in light of their unique characteristics and the disproportionate impact the proposed new pricing rules will have on these therapies. This working group, which would include rare disease innovators, would run case studies involving rare disease treatments to better understand how the new pricing framework would apply concretely to these therapies. It would also provide the opportunity for working group participants to recommend triggers for the application of pricing tests, pricing formulas and pricing floors that are appropriately suited for rare disease treatments.

This is an extremely exciting time for the rare disease community given the incredible scientific and technological advances underway. However, the benefits of many of these technologies will not reach Canadian patients in a timely manner if the guidelines are adopted without change. We hope that the PMPRB will work with RAREi, industry associations and other health system stakeholders to find a better approach that would position Canada as an example to follow internationally in terms of providing timely access to rare diseases treatment and a place to pursue real innovation.

We thank you again for the opportunity to provide our input, and look forward to working with you to build a pricing review framework that achieves sustainability for our health care system while still

allowing companies, such as RAREi members, to bring the value of their medicines and clinical trials to Canada, for the benefit of the Canadian rare disease community.

Yours sincerely,

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RAREi's Submission on PMPRB's Draft Guidelines

1. Background on rare diseases

As biopharmaceutical companies committed to improving the lives of patients living with rare disorders by researching, developing and commercializing rare disease treatments, we can attest that developing treatments for rare disorders is an extremely risky and costly endeavour.

The investments made to develop a new rare disease treatment must be recouped from a much smaller pool of patients compared to medicines for common diseases. As a result, rare disease treatments tend to be priced higher than medicines for common diseases.

However, while rare disease treatments generally result in higher initial per-patient costs, their overall budget impact is comparatively low given their small patient populations. According to an analysis presented at the 2019 ISPOR Conference, public expenditure for rare disease medicines in Canada represented less than 2% of total Canadian government spending on medications in 2018, and is expected to continue to represent less than 7% by 2025.[1]

A recent academic study by the Canadian Health Policy Institute (CHPI) also demonstrated that the costs and prices of patented medications have been stable and moderate for the past twenty years.[2]

These studies show that growth in the cost of medications, including rare disease treatments, is not unstainable and will not bankrupt the public health system, as some have suggested incorrectly.

Further, it should be emphasized that it is already very difficult to commercialize new rare disease treatments in Canada under the current pharmaceutical review system. In fact, a recent study shows that many rare disease therapies are launched in Canada at a much later time than in the United States and/or Europe and, in many cases, they are not even available to patients in

[1] Forte L et al, *The current and future cost of orphan drugs in Canada*, Poster at ISPOR Europe 2019, Copenhagen, Denmark, November 2019. https://www.ispor.org/heor-resources/presentations-database/presentation/euro2019-3122/96632

[2] Canadian Health Policy Institute (CHPI). Facts about the cost of patented drugs in Canada: 2018 Edition. *Canadian Health Policy*, February 2019: https://www.canadianhealthpolicy.com/product_articles/facts-about-the-cost-of-patented-drugs-in-canada--2018-edition-.html.

Canada.[3] This is because no aspect of the reimbursement process, including regulatory review and approval, pricing review, health technology assessments, product negotiations or funding frameworks are set up to appropriately evaluate these treatments. Moreover, the current review and approval process is ill-prepared to respond effectively to the new innovative trial designs and adaptive studies that are common when researching new rare disease treatments. The challenges in assessing new orphan treatments is unfortunate in light of the fact that the science is evolving quickly and innovators are increasingly able to produce more targeted treatments for patients, which will drive better health outcomes and help offset other health care and societal costs.

As a result of these challenges, Canadians affected by rare disorders, which are often severe and debilitating, struggle immensely to access the treatments they need to survive or get better. This is in addition to the multiple other challenges faced by rare disease patients, including a very long journey to reach a diagnosis due to lack of disease awareness, small patient populations, fewer health care resources available to treat the conditions and many unknowns about the disease. As well, for many rare disease patients, there are no medicines available yet to treat their condition.

The new rules proposed by the Patented Medicine Prices Review Board (PMPRB) will significantly exacerbate the current challenges facing rare disease patients, innovators and health systems.

2. Negative implications of new price controls

A recent case study supported by RAREi reviewed the impact of the draft PMPRB guidelines on the commercialization of a rare disease therapy. It found that a manufacturer would have to reduce its price between 45% to 75% to comply with the PMPRB's proposed rules.[4] In addition, a PDCI Market Access analysis of the impact of the federal pharmaceutical price control reforms found that rare disease medicines would be facing an average price reduction of 80%.[5] These levels of price reduction are much higher than what Health Canada forecasted in its revised Cost Benefit Analysis that accompanied the regulatory amendments. Specifically, while Health Canada indicated that the financial impact would be $8.8 billion over 10 years, the PDCI analysis calculated that the impact would be closer to $41.8 billion.[6]

Based on their own internal calculations, RAREi members can confirm that similar or even more severe price reductions would be required to comply with the new pricing rules. Such drastic price reductions will deter many innovators from bringing new medicines to Canada. This will be

[3] Rawson, N., Fraser Institute, *Regulatory, Reimbursement, and Pricing Barriers to Accessing Drugs for Rare Disorders in Canada*, 2018: https://www.fraserinstitute.org/sites/default/files/barriers-to-accessing-drugs-for-rare-disorders-in-canada.pdf.

[4] Rawson, Nigel SB; Lawrence D., *New Patented Medicine Regulations in Canada: Updated Case Study of a Manufacturer's Decision-Making about Regulatory Submission for a Rare Disorder Treatment*, Canadian Health Policy, 2020: https://www.canadianhealthpolicy.com/products/new-patented-medicine-regulations-in-canada--updated-case-study-.html.

[5] PDCI Market Access, *Impact Analysis Of The Draft PMPRB Excessive Price Guidelines*, February 12, 2020.: http://www.pdci.ca/wp-content/uploads/2020/02/PDCI-PMPRB-Impact-Assessment-February-2020_Final.pdf.

[6] Ibid.

particularly damaging to rare disease innovators, many of which are small and medium-sized Canadian biotechnology companies. Given their more limited resources, it will be harder for them than larger pharmaceutical companies to: 1) absorb such price reductions in the context of more limited product portfolios; 2) provide treatments on compassionate grounds and 3) comply with the new burdensome rules.

Further, if Canada becomes a late-tier launch country globally as a result of the new price controls, it will become significantly more challenging for innovators to undertake research here, including clinical trials. This means that numerous research institutes, academic health centre research arms, contract manufacturing and research operations, early-stage pharmaceutical developers and the support system that nurtures them will be challenged to maintain their presence in this country.

A recent survey by Research Etc. canvassed life sciences executives and confirmed that the pricing reform will have serious negative consequences. Specifically, according to the survey results, more than 90% indicated that the reform will lead to fewer product launches, delays in launches and will have a negative impact on research investments and employment in Canada.[7]

3. Key problematic aspects of the draft guidelines

Inappropriate use of economic factors to set market prices

While RAREi recognizes that pharmacoeconomic (PE) and budget impact data can be used as tools to help inform reimbursement decisions for certain treatments, they should not be used to establish hard pricing ceilings in a regulatory context, especially for rare disorder treatments. There are many reasons for this, including:

- The use of hard cost per quality-adjusted life year (QALY) thresholds is very controversial and it is impossible to find agreement on what these thresholds should be, how they are calculated and could be adjusted for rare disease treatments.
- Standard PE methods used in health technology assessments (HTAs) are not well-suited for evaluating rare disease treatments given the smaller size and type of clinical trials conducted, which often lead to greater uncertainty compared to treatments for more common illnesses. In fact, many experts have recognized the limitations of using QALY analyses, especially as it pertains to rare disease treatments. According to a study that reviewed the impact of QALYs on the assessment of ultra rare disease (URDs) medicines, "many interventions for rare and URDs are unlikely (or altogether unable) to meet standard cost per QALY benchmarks." It concluded that there is a strong need for alternative economic evaluation models for URDs.[8] This is why the vast majority of Canadian Agency for

[7] Research Etc., *Impact of PMPRB Pricing Changes*, Life Sciences Ontario, February 3, 2020: https://lifesciencesontario.ca/wp-content/uploads/2020/02/Research-Etc.-PMPRB-Survey-02-03-20.pdf.

[8] Schandler M et al, *Incremental cost per quality-adjusted life year gained? The need for alternative methods to evaluate medical interventions for ultra-rare disorders.* Journal of Comparative Effectiveness Research: Res. (2014) 3(4), 399–422: https://www.ncbi.nlm.nih.gov/pubmed/25275236. See also

Drugs and Technologies in Health (CADTH) evaluations of rare disease treatments find these treatments not to be cost-effective and often recommend price reductions of more than 90%.

- It would be inappropriate to use QALY-driven incremental cost-effectiveness ratios (ICERs) developed by CADTH in the context of price setting given their significant variability and subjectivity. For instance, we see wide variations of ICERs between CADTH and manufacturers because CADTH reinterprets the manufacturer-submitted ICERs using the same economic model, but altering the assumptions. In most cases, resulting CADTH ICERs bear little, or no, resemblance to those originally submitted by manufacturers. CADTH's re-interpretations are not subject to correction, oversight or validation by anyone outside of CADTH's review process. Also, while CADTH has full license to comment on manufacturers' reimbursement dossiers and PE models, it limits manufacturers' ability to comment on CADTH reviewers' reports and PE re-analyses with a fixed-size template. Finally, it issues recommendations that do not include manufacturers' positions on CADTH's re-analyses of PE models and often do not reflect clinical realities or current medical practice. Also, we see wide variations of ICERs between CADTH and other HTA agencies, such as Quebec's Institut national d'excellence en santé et en services sociaux (INESSS).

Currently, the way that uncertainty in HTA analyses are addressed is through national negotiations that follow the CADTH review process. On behalf of public payers in Canada, the pan-Canadian Pharmaceutical Alliance engages manufacturers in good faith negotiations that result in confidential prices that are manageable for both parties. This process is comparable to pricing mechanisms in many comparable countries internationally. The PMPRB's proposed attempt to apply pharmacoeconomics as a means to regulate prices and the resultant downward price pressure does not exist in any other country.

In addition to our concerns about the reliance on pharmacoeconomics as part of the price regulation system, we also object to the use of market size to further ratchet down the prices of medicines. This factor is completely irrelevant and disconnected to the PMPRB's mandate of determining price excessiveness and should not be used in tests to set pricing ceilings.

Lack of a pricing floor creates significant uncertainty

The calculation of the maximum rebated price (MRP) does not include a pricing floor. This, along with the use of uncertain and variable economic factors as discussed above, will make it very challenging, if not impossible, to predict what the ultimate price ceiling is likely to be in Canada.

Given the dynamics of pharmaceutical pricing internationally, global head offices will want to understand what the Canadian price is likely to be before planning to introduce a medicine in this country. Without assurances that they can reasonably rely on a particular price point within a pricing corridor for countries with comparable health care systems or standards or against which other countries will compare, they will likely decide not to introduce their medicines in Canada or

National Council on Disability, *Quality-Adjusted Life Years and the Devaluation of Life with Disability,* November 6, 2019: https://ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf.

will launch their medicines at a much later time in the global launch sequences. Further, the lack of a price floor could lead to unreasonably low prices, even as low as $0 in some cases.

We suggest that the PMPRB consider reasonable price floors in addition to ceilings in order to improve predictability for innovators.

Lack of accommodation for rare disorders inconsistent with provincial/federal initiatives

The draft guidelines allow the PE price (PEP) of a rare disorder medicine to be increased by 50% for the first $12.5 million of annual sales. However, this increase will be of little benefit to rare disease innovators given the that the PEP will be set at an unreasonably low level based on the proposed PE pricing test, which uses an artificially low pharmacoeconomic value threshold (PVT).

Further, while we do not support the use of PVT in PMPRB's pricing review framework, we note that the PMPRB had initially proposed a higher PVT for rare disease treatments in its Guidelines Scoping Paper.[9] The PMPRB has since abandoned this distinction and is now applying the same extremely low PVT to all treatments, including rare disease treatments.

In sum, the PMPRB's new pricing guidelines fail to make appropriate accommodations that are required given the unique characteristics of rare disease treatments. Under the proposed framework, all rare disease therapies would likely be classified as "Category 1 drugs" and would be subject to the same draconian price controls as other medicines, except for the 50% price premium that will be of little utility in supporting patient access to these medicines.

Further, medicines provided through Health Canada's Special Access Programme (SAP) will also be subject to the new price controls. This will especially hurt rare disease patients, as many of them currently rely on the SAP to access their treatments.

It is surprising that the PMPRB opted to take this approach given the increasing willingness of Canadian governments to find ways to facilitate the reimbursement of, and improve access to, rare disease therapies:

- The federal government has committed to spearheading and funding a national rare disease strategy, recognizing that "special consideration" is required to ensure a nationally consistent approach for these medications."[10]
- There are ongoing active efforts at the provincial-territorial level to find new approaches to improving publicly funded access to rare disease medicines via the Expensive Drugs for Rare Diseases Working Group.[11]
- Quebec indicated that improving access to rare diseases is a provincial priority and that it plans to pilot test the application of a customized evaluation framework for rare disease

[9] PMPRB, *Guidelines Scoping Paper*, 2017: https://www.pmprb-cepmb.gc.ca/view.asp?ccid=1341.
[10] Government of Canada, Budget 2019: https://www.budget.gc.ca/2019/docs/plan/toc-tdm-en.html.
[11] Please note that RAREi objects to the name of the working group given its characterization of all rare disease treatments as "expensive". We would prefer that the working group name be changed in order to engender a less pejorative tone towards these important treatment options.

treatments in the next few years.[12] INESSS has recently broadened the lens through which it assesses the value of rare disease medicines by introducing the notion of "promising value".[13]

- Ontario has stated it would like to see federal/provincial discussions on pharmacare focused on finding a solution for rare disease treatments.[14]

Lack of rewards to encourage innovation

The existing PMPRB guidelines provide pricing incentives for innovators that commercialize medicines with a higher level of clinical improvement. However, the new draft guidelines do not recognize varying levels of innovation among medicines. We believe that this is a significant oversight, particularly in the context of rare diseases, where new therapies are desperately needed and can dramatically improve patients' lives.

We believe it is important that the PMPRB's pricing framework recognize advances in innovation by rewarding innovators for progress made in addressing medical needs.

New reporting rules could jeopardize patient access programs

Given that the regulatory amendments would now require patentees to report price and revenue information net of all price adjustments, including direct and indirect discounts, we are concerned that the PMPRB will treat all products provided via compassionate access programs as zero dollar sales for the purposes of calculating the maximum list price (MLP) and the MRP.

This would have a direct deflationary impact on allowable prices, which would discourage manufacturers from providing patients with complimentary coverage through any mechanism, including through clinical trials, corporate compassionate access programs and Health Canada's SAP.

The PMPRB has had an existing free goods policy in place since April 2000 that was intended to reduce the risk of discouraging manufacturers from offering free goods to patients on a compassionate basis or for supplying medicines for clinical trials.[15] RAREi encourages the PMPRB to maintain a similar policy when applying its new guidelines.

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[12] INESSS, *Plan triennal d'activités 2019-2022*: https://www.inesss.qc.ca/fileadmin/doc/INESSS/DocuAdmin/INESSS_PTA_2019-2022.pdf.

[13] INESSS, *Advice to the minister regarding Galafold*: https://www.inesss.qc.ca/fileadmin/doc/INESSS/Inscription_medicaments/Avis_au_ministre/Novembre_2018/Galafold_2018_10.pdf.

[14] Gibson, V., *Elliott says Ontario doesn't want full pharmacare overhaul, urges focus on drugs for rare diseases*, IPolitics, November 21, 2019: https://ipolitics.ca/2019/11/21/elliott-says-ontario-doesnt-want-full-pharmacare-overhaul-urges-focus-on-drugs-for-rare-diseases/.

[15] PDCI: http://www.pdci.ca/pmprb-and-zero-dollar-sales/.