RAREi
THE CANADIAN FORUM FOR
RARE DISEASE INNOVATORS

RAREi Submission

Draft Guidelines for PMPRB Staff

March 19, 2025

The Canadian Forum for Rare Disease Innovators (RAREi) appreciates the opportunity to comment on the draft price review guidelines prepared by the Patented Medicine Prices Review Board (PMPRB) for feedback.

RAREi is a network of 19 innovative biopharmaceutical companies dedicated to improving the lives of patients with rare diseases by developing and commercializing treatments. Since its establishment in 2018, RAREi has participated in all Health Canada and PMPRB consultation opportunities related to modernizing the *Patented Medicines Regulations* and the board's guidelines. **Its key message throughout has been the need to consider the particular challenges associated with developing and commercializing treatments for small populations.** RAREi submissions are available on its website: www.rarei.ca.

Introductory remarks

In keeping with RAREi's feedback offered during Phase II of the board's effort to create a less intrusive and more streamlined approach to addressing potentially "excessive" prices for patented medicines in Canada, the members continue to be supportive of the broad outlines of the new approach, particularly its intention to respect the board's limited mandate as articulated in recent court decisions issued by the Quebec Court of Appeal and the Federal Court of Appeal. RAREi also appreciates the more pragmatic process for evaluating whether a price should be subject to an in-depth review.

However, there remain a series of refinements to the draft guidelines that should be considered, especially in recognition of the unique circumstances faced by rare disease treatment innovators as they seek to introduce new solutions for rare disease patients. To be specific, throughout the last several years of PMPRB's regulatory modernization efforts, the board has never acknowledged or accounted for the additional challenges represented by rare disease treatment development. RAREi hopes this can be remedied before the guidelines are finalized.

Previous RAREi submissions to the board have described the enormous challenges faced by rare disease patients, families and caregivers, who, in addition to coping with severe and debilitating rare disorders and disruptions to their daily lives, also must manage through long diagnostic odysseys, uncertain access to clinical trials, difficulties associated with meeting patient needs when they have conditions that affect small patient populations, limited health care resources available to treat those conditions, many unknowns about the disease and, of course, restricted access to needed treatments.

On that latter point, it is important to appreciate that Canada performs relatively poorly compared to other developed countries when it comes to facilitating access to important treatment advances. The reality is that only 60% of innovative treatments for rare disorders introduced globally are approved by Health Canada. And when authorized, it can take up to six years longer than in the United States and Europe for them to become available for

patients.[1] Even when approved and launched, patients face challenges in securing public funding. The time between regulatory approval and listing on public provincial formularies averaged 736 days in 2022, double the average time reported in comparable countries.[2] As well, there is a significant difference in reimbursement timelines between public and private drug plans in Canada, which is significant for the rare disease community because the vast majority of rare disease treatments are reimbursed by public payers. According to one study, private plans take 142 days on average to cover new medicines following Health Canada's approval compared with 449 days for public drug plans.[3] As a result, many people with rare disorders in Canada are missing out on treatments that could save or significantly improve their lives.

While the review and approval process for new medicines is not directly relevant to the PMPRB's mandate, nevertheless, it is important for the board to appreciate the impact that those processes have on rare disease patients and their families, as well as orphan treatment developers. Rare disease innovators face a lot of uncertainty when bringing new solutions into the Canadian market, including a complex and lengthy journey from introduction to reimbursement, high upfront costs and a lack of targeted incentives available in other markets that are designed to promote rare disease product development and launch. These challenges are more acutely felt by rare disease treatment developers that are small biotech firms, including Canadian companies. The proposals for annual reviews, for example, will be particularly burdensome on smaller companies, by forcing them to constantly monitor exchange rates and prices across many markets.

The situation and receptivity for orphan medicine developers is different in other developed countries, which provide such things as enhanced intellectual property protection, fee waivers and regulatory and reimbursement policies customized to address the specific challenges of developing treatments for small patient populations.

In this context, RAREi urges the board to consider how it can best meet its objectives without imposing additional burden on innovators or negatively affecting bigger and more influential markets. Rare innovators operate in a global pharmaceuticals market, in which Canada is a minor player. Sector leaders play a vital advocacy role for the Canadian market in the context of global imperatives that are driven by much bigger countries and regions.

The board should keep in mind that Canada often serves as a direct and indirect pricing benchmark for other markets which means that Canadian prices must be consistent with global pricing frameworks or be subject to negative consequences as corporate decision-making prioritizes higher priority markets. The key take-away is that a Canadian price that is set too low can make a Canadian general manager's case for bringing a medicine to Canada untenable.

This is a particularly important consideration in light of the economic upheaval facing Canada, and indeed the world, in the face of a growing trade war between the United States and Canada which, in part, appears focused on forcing manufacturers to relocate operations to the US at the expense of the rest of the world. Multiple tariff threats have been floated and/or implemented, any of which could affect cross-border trade in pharmaceuticals. With some predictions that the Canadian dollar will fall significantly in relation to the US and European currencies, continuing to avoid regulatory actions by the PMPRB will be a constant challenge, especially if it is unclear how the guidelines will be applied.

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[1] Ward L et al, An international comparative analysis of public reimbursement of orphan drugs in Canadian provinces compared to European countries, *Orphanet Journal of Rare Diseases*, March 4, 2022: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8895096.

[2] Conference Board of Canada, Access and Time to Patient Prescription Drugs in Canada, January 4, 2024: https://www.conferenceboard.ca/wp-content/uploads/2022/10/access-and-time-to-patient_jan2024.pdf.

[3] Canadian Health Policy Institute, Coverage of new medicines in public versus private drug plans in Canada 2008-2017, 2018: https://www.canadianhealthpolicy.com/product/coverage-of-new-medicines-in-public-versus-private-drug-plans-in-canada-2008-2017-2

With this in mind, RAREi has supported the publication of peer-reviewed orphan-medicine-related case studies to evaluate previous guidelines drafts.[4],[5] These analyses determined that a "high level of uncertainty being generated by the changes in the PMPRB's draft guidelines will imperil the launch of all new medicines in Canada because it will significantly decrease the attractiveness of the country as a jurisdiction in which pharmaceutical companies seek regulatory approval for new products."

It has also called for the PMPRB to organize and host case study reviews involving industry players and board staff before the guidelines are finalized to assess the impact of its proposed changes on potential pricing based on specific scenarios. To clarify, this approach is different than the staff-generated case studies published with the draft guidelines. While helpful in demonstrating the mechanics of the proposed approach to price reviews, the case studies outlined in the draft do little to address how the guidelines will function when the board is faced with unique challenges represented by a new orphan treatment. Critically, the case studies need to consider what an innovator faces when determining when and whether to bring a new patented rare disease treatment to Canada. RAREi requests that such collaborative reviews take place based on the next iteration of the guidelines before they are implemented and would be pleased to work with PMPRB staff on any technical working groups that are organized.

With those preliminary remarks in mind, this submission will now address some of the proposals outlined in the draft. The following sections correspond to the draft document sections.

Overview of the PMPRB and its Legislation

RAREi supports the board's shift away from trying to establish and enforce an acceptable price point for each product to an approach that defines a process for assessing whether additional review might be required to identify cases of potential price excessiveness.

While RAREi appreciates the board's determination that it should not attempt to approve an acceptable price and the effort to improve the brevity and clarity of the initial price review process, it is of the view that a completely hands-off approach by staff is not helpful either. Predictability in the context of a PMPRB review would increase Canada's attractiveness as a place for new medicines to be launched that many Canadians with rare diseases badly need. Therefore, for planning purposes, some general direction from staff should be available to innovators who wish to test their pricing assumptions as they launch new medicines or consider price changes.

RAREi acknowledges that the board is the ultimate arbiter of whether a price would be deemed excessive, without being fettered by the guidelines per se. However, in order to support rational operational and commercial business planning, board staff should be in a position to provide direction to rights holders based on some general parameters that would be considered by the board in subsequent in-depth price reviews and hearings.

Review Process

RAREi supports the board's proposal to limit the initial price review to a comparison of prices in the PMPRB11, and to conduct that initial assessment only after the product is available in other markets. However, RAREi proposes that no initial price comparison (IPC) should be conducted until list prices are available in at least five PMPRB11 countries and that at least one is the UNited Kingdom, Italy, or Japan. Undertaking an IPC when prices are available in just one or a

[4] Rawson N, *New Patented Medicine Regulations in Canada: Case Study of a Manufacturer's Decision-Making about Regulatory Submission for a Rare Disorder Treatment*, Canadian Health Policy, October 2018: https://www.canadianhealthpolicy.com/download-article/1642/0.

[5] Lawrence D & Rawson N, *New Patented Medicine Regulations in Canada: Updated Case Study*, Canadian Health Policy, January 2020: https://www.canadianhealthpolicy.com/product/new-patented-medicine-regulations-in-canada-updated-case-study-en-fr-2.

few lower-priced jurisdictions raises the likelihood that a Canadian price will be higher than the highest international price (HIP) within the PMPRB11 only to later be found to be below the standard when higher-priced countries are added to the calculation. It makes sense to ensure that prices from a mix of comparative countries be considered to avoid unnecessary in-depth reviews based on incomplete data.

Moreover, as RAREi has stated before, not every product identified as having a list price higher than the HIP should be referred for an in-depth review automatically. Where there is clear unmet need or a gap in particular therapeutic areas and when there is a public policy rationale to support it, higher list prices than the HIP could be warranted as a means of encouraging the commercialization of new rare disease medicines in Canada. Provision should be made in the guidelines for rights holders to make a case to staff for a list price that may be higher than the HIP before an in-depth review is initiated, for example, when the product is only available through public procurement and negotiation processes.

In addition, the guidelines should address explicitly how the staff will address scenarios where the US is the only potential comparator country. This is the circumstance that many rare disease products are in now and it can be expected to be the case for many products going forward.

Regarding the consideration of consumer price index (CPI) changes as part of the annual review, RAREi feels that the reliance on a one-year lagged CPI adjustment is too limited to account for volatile inflationary times. In addition, some jurisdictions require a price increase notification be provided before the annual CPI rate is published by Statistics Canada. For example, to take a price increase in April 2026 (standard timeframe for most jurisdictions), notification would be required in December 2025. However, the 2025 CPI rate would not be published by Statistics Canada until January 2026, which does not correspond with the timing of the notification requirement. The PMPRB's previous three-year CPI adjustment factor has proven to be an effective way to moderate the effects of inflationary shifts over time and should be retained.

Also, in an effort to improve the predictability of the price review process, and avoid innovators being required to respond to every price shift within the PMPRB11, RAREi proposes that the annual review of prices in the years after launch should only be reviewed against CPI changes. If the medicine's price has not increased beyond the adjusted-CPI level, it should not be subject to referral for an in-depth review. No further IPC should be conducted unless there is a significant change in prices across a number of comparator countries.

For similar reasons, RAREi requests that the board reconsider its decision to make existing medicines that have previously been deemed compliant with PMPRB's guidelines subject to an IPC when the new guidelines are implemented. Products marketed prior to July 1, 2022 that are priced at or below the previously accepted non-excessive average price on the implementation date, and which did not increase beyond CPI in the meantime, should not be subject to referral for in-depth review as long that the list price remains within a CPI adjusted amount. This is a matter of procedural fairness (they were commercialized under a different regulatory regime), practicality (the PMPRB could focus on go-forward challenges) and common sense (products that were not excessive in the first half of 2022 should not be flagged as potentially excessive in 2025).

RAREi believes that imposing new pricing rules on existing medicines would also lead to significant operational challenges and could result in supply disruptions. Most existing products are already subject to effective price-lowering mechanisms through pan-Canadian Pharmaceutical Alliance (pCPA) and health benefit provider negotiations and subject to product listing agreements that could be disrupted by new prices. Such products should be exempt from IPCs and the potential for an in-depth review unless a valid complaint is made.

Regarding the complaints process outlined, RAREi believes that the right to make a complaint should be limited to the federal minister of health or any of his/her provincial or territorial counterparts only. Others who believe that a product price should be reviewed could submit those concerns to the minister(s) for consideration and rely in them to determine if there is a case to be made to the board via an official complaint. The ministers are the best positioned to assess whether a complaint is relevant to the board's limited mandate. Moreover, the public and private payers have existing mechanisms in place to protect consumers' interests and deal with price concerns effectively without the need to rely on PMPRB's support.

As for the complaints received, RAREi does not concur with the PMPRB proposal to automatically refer any product that is the subject of a complaint for in-depth review. Some form of validation is needed to assess whether the product that is the subject of complaint is based on a legitimate concern about a product list price. That review should be focused on ensuring that vexatious or irrelevant complaints, for example, or those out of the jurisdictional scope of the PMPRB, are not considered. The current complaints process, for example, provides a process for a preliminary examination of the price by board staff to determine if the price "appears excessive," before an investigation is opened.

In-Depth Review

While RAREi appreciates the sentiment expressed in the draft that no pre-supposition of excessiveness would be made by staff, it remains concerned about the potential for too many in-depth hearings to be recommended. What continues to be missing from the draft, is any indication that staff will engage formally with rights holders before making its in-depth review recommendations (as well as when a hearing is recommended).

The process as proposed gives too much discretion to staff, particularly in terms of determining the appropriate therapeutic class comparators, without giving any formal opportunity to rights holders to contribute. To RAREi, a staff option to engage with and hear from rights holders is not sufficient. There must be a clear and defined process of dialogue for the board staff to follow before any recommendation is made. A commitment by the board that staff would be required to rely on dialogue and collaboration with rights holders to address any differences regarding whether a product should be recommended for an in-depth review and/or a hearing is a vital step that should be added to the process, particularly when considering orphan medicines.

As RAREi stated previously, it believes that a robust dialogue between the rights holder and board staff should almost always be sufficient to arrive at a reasonable understanding. With that in mind, dialogue and collaboration between the rights holder and board staff should be explicitly stated in the guidelines as the operating culture and preferred method for addressing disputes regarding what should be a considered for an in-depth review and which products should be recommended to the chair for a hearing.

Regarding the selection of therapeutic comparators, RAREi believes that the chosen comparators must be selected very carefully and attention should be given to ensuring that the new treatments are not being equated with out-dated, unsuitable or irrelevant alternatives. Once again, the specific challenges associated with assessing rare disease treatments must be accounted for when determining the appropriate comparator.

RAREi appreciates the board's attempt to allay concerns about reliance on inappropriate comparators by assigning a level of similarity to the patented medicine under review using a two-step framework. While that proposed approach is supported and represents an improvement, it does not go far enough.

In the past, RAREi has proposed the replacement of the Human Drug Advisory Panel (HDAP) with a different approach to defining the appropriate comparator, particularly in the case of orphan treatments. RAREi members would like to

see a mechanism for standing up customized panels comprised of independent, arms-length expert clinicians (not by PMPRB staff) to make that determination.

RAREi believes that expert clinical advice is required and should be sought by board staff in every case when a therapeutic class comparison is undertaken. However, that expert advice should be as closely relevant to the product and therapeutic areas under review as possible. Therefore, in each case, a separate independent panel of clinicians who are familiar with the condition and have expertise in managing patients directly should be called upon to identify the appropriate comparator. RAREi also believes that those expert opinions should be binding on PMPRB staff.

In the past, RAREi members' have experienced situations where the comparators identified by staff and the HDAP have been questionable and/or inappropriate products that have resulted in highly problematic price points being deemed compliant. Those negative experiences have included the PMPRB's reliance on inappropriate or irrelevant comparators, such as unapproved products, without any link to clearly defined scientific evidence evaluation methods and which have been questioned by clinical experts.

Regardless of the method of identifying comparators, RAREi holds the position that they should not include generics, biosimilars or non-prescription or non-approved treatments within the class. Comparing new innovative products to a class that includes such products undermines any incentives to research and launch new medicines in an existing class of products. The suggestion that price comparisons would be made within a therapeutic class without any recognition of the numerous evolutions in treatment that emerge all the time is non-sensical. That would mean that allowable prices would not distinguish between modern, cutting-edge treatments and older, often long-genericized medicines. By ignoring such improvements, and the clinical and quality-of-life improvements that arise from them, the board will undermine the innovation process and discourage medical progress. If the PMPRB decides to include generics and biosimilars for domestic and international therapeutic class comparisons, the board should allow for the highest price in the class as the relevant threshold.

RAREi appreciates the opportunity for rights holders to prepare and submit an undertaking during an in-depth review and the time between a staff recommendation for a hearing and the chair's decision in that regard. It believes that addressing identified pricing issues through undertakings designed to address staff concerns about list price excessiveness is a pragmatic and appropriate way to administer the regulations. That way, a hearing may be required only in the rare event of an inability to reach an agreement.

Conclusion and Recommendations

RAREi is pleased that PMPRB is committed to remaining focused on its core mandate which is to operate as a passive oversight agency that guards against an abuse of market exclusivity, especially in light of the existence of many other price-moderating and value-generating initiatives across Canadian public and private payers. RAREi also believes that the board must undertake its oversight responsibility with care to avoid dissuading innovators from undertaking the research, development and commercialization of important treatments for Canadians and the world.

In particular, RAREi wants to see guidelines that are designed to reduce uncertainty for rare disease developers in order to ensure that orphan patients have rapid and publicly supported access to the incredible scientific and technological advances underway as soon as possible. That requires the PMPRB guidelines to be crafted carefully and in a way that would position Canada as an example to follow internationally in terms of providing timely access to rare disease treatments and a place to pursue real innovation.

Thank you for your consideration. RAREi looks forward to working with the PMPRB, industry associations, patients, clinicians and other health system stakeholders to truly modernize the patented pharmaceutical price review process in Canada.

About RAREi

RAREi is a network of biopharmaceutical companies dedicated to improving the lives of patients with rare diseases by developing and commercializing treatments. This network includes the following members: Alexion Pharma Canada, Amgen Canada, Amicus Therapeutics Canada, argenx Canada, Biogen Canada, BioMarin Pharmaceutical (Canada), Boehringer Ingelheim Canada Ltd., Ipsen Biopharmaceuticals Canada, Johnson and Johnson Innovative Medicines Canada, Medison Pharma Canada, Mitsubishi Tanabe Pharma Canada, Medison Pharma Canada, PTC Canada, Recordati Rare Diseases Canada, Sanofi Canada, Sobi Canada, Takeda Canada, UCB Canada, Ultragenyx Pharmaceutical and Vertex Pharmaceuticals (Canada). For more information, please visit www.rarei.ca.