RAREi
THE CANADIAN FORUM FOR
RARE DISEASE INNOVATORS

RAREi Submission on Updated PMPRB Guidelines

Shaping the Future: A Discussion Guide for PMPRB Phase 2 Consultations on New Guidelines

September 2024

The Canadian Forum for Rare Disease Innovators (RAREi) appreciates the opportunity to offer feedback and insights in response to the Patented Medicine Prices Review Board's (PMPRB's) June 2024 discussion paper as part of the second phase of consultations on new price review guidelines for rights holders.

RAREi is a network of 17 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 consistently 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 for consideration of the particular challenges associated with developing and commercializing treatments for small populations.** RAREi submissions are available on Its website: www.rarei.ca.

Introductory remarks

To begin, RAREi appreciates the careful and consultative approach that the board and its staff have taken in developing new guidelines. In addition, RAREi acknowledges and endorses the board's determination to limit its scope to a strict interpretation of its legislative mandate and to focus its price assessments primarily on the four comparative factors outlined in the *Patent Act*. Finally, RAREi is fully supportive of the more streamlined process for evaluating whether a price should be subject to further review, including reserving any therapeutic class comparisons until the in-depth review phase. This corresponds with RAREi's previous recommendations that the board stick to its constitutionally appropriate knitting, that it take a pragmatic approach to price reviews and ensure that rights holders are provided with the certainty required to invest in research and commercialization of new medicines in Canada.

For context, RAREi wishes to share some of the unique challenges faced by rare disease patients, families and caregivers. The reality is that many Canadians affected by often severe and debilitating rare disorders struggle to access needed treatments. This is in addition to the multiple other challenges they face, including the very long journey to reach a diagnosis, uncertain access to clinical trials, the difficulties associated with meeting patient needs when they have conditions that affect small patient populations, limited health care resources available to treat those conditions and many unknowns about the disease. For many rare disease patients, there are no treatments available yet to treat their condition. That is why it is important to ensure that those that are developed can be made available to patients who need them as soon as possible.

Evidence exists demonstrating that rare disease therapies are launched in Canada much later than in the United States and/or Europe and, in many cases, new innovative treatments are not made available for patients in Canada. To put things in perspective, fewer than two-thirds of the rare disease treatments approved in Europe were submitted to Health Canada for regulatory approval, and among those approved by Health Canada, the rate of public

reimbursement is low.[1] Meanwhile, only 54% of rare disease treatments approved by Health Canada are subsequently reimbursed by public drug plans in Canada.[2]

In addition to the patient and caregiver struggles, new orphan treatment innovators are challenged by the high degree of uncertainty associated with bringing new innovations to market. There are high upfront costs associated with doing business in Canada and it lacks the targeted incentives that are typically offered in other developed countries to encourage rare disease product development and launch, such as enhanced intellectual property, regulatory and reimbursement policies. Europe, the United States and many other developed countries have implemented policies to offset the business and clinical challenges that a small number of patients represents compared with medicines for common diseases. The federal government's National Drugs for Rare Diseases Strategy goes some way to encouraging provinces and territories to fund new rare disease therapies and diagnostics faster, however, there are many other tools in the federal toolbox that have not been used which are commonplace in other parts of the world.

On the pricing side, it must be understood clearly that Canada is often serves as a benchmark for other markets – meaning that Canadian prices have a follow-on impact on higher population markets. According to a World Health Organization report, Canada is a reference country for Brazil, South Africa, Taiwan, Egypt, Saudi Arabia and the United Arab Emirates. Canadian prices are also indirectly referenced. For example, China references Taiwanese prices for some products and some Latin American countries reference Brazil. In addition, some European countries informally reference Canada if it is the first country of launch (or second after the US).[3] Corporate decisions about when (or even whether) to bring medicines to Canada are necessarily sequenced to optimize market opportunities around the world.

Traditionally, the PMPRB has represented a substantial challenge for rare disease innovators in that the effective price ceilings permitted have often represented major obstacles to launching in Canada even before the changes to the regulations that prompted this consultation.

In the past, the PMPRB has attempted in several cases to dictate price ceilings that are the lowest among comparator countries. In the absence of any public consultations related to that approach, at least six voluntary compliance undertakings have been completed using the lowest price standard in recent years.[4] Any further imposition of "lowest of" benchmarks will continue to send challenging signals to rare disease developers that deploying medicines in Canada may be subject to onerous and uncertain price controls. A price ceiling that is set at too low a level can, for obvious reasons, make the case for bringing a medicine to Canada untenable.

So far, the PMPRB's regulatory modernization efforts have never acknowledged or accounted for the additional challenges represented by rare disease treatment development. With this in mind, RAREi has supported the undertaking of several published and peer-reviewed case studies to evaluate previous guidelines drafts,[5],[6] and stands ready to do the same with updated draft guidelines when they are published.

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[1] Ward et al, *An international comparative analysis of public reimbursement of orphan drugs in Canadian provinces compared to European countries*. Orphanet Journal of Rare Diseases, Issue 17, Article 113, March 4, 2022): https://doi.org/10.1186/s13023-022-02260-6.

[2] Rawson N, *Availability and Accessibility of Essential Drugs for Rare Disorders in Canada*. Canadian Health Policy, October 13 2021: https://doi.org/10.54194/HFEB4050 www.canadianhealthpolicy.com.

[3] Dedet G. *Pharmaceuticals Pricing and Reimbursement Policies in Europe,* WHO TBS, October 2016.

[4] PMPRB, Voluntary Compliance Undertakings, (accessed September 3, 2024: https://www.canada.ca/en/patented-medicine-prices-review/services/voluntary-compliance-undertakings.html.

[5] 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.

[6] 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.

Unfortunately, the case studies included in the discussion paper do not achieve what RAREi was looking for when it proposed the undertaking of a case study approach to pressure test new guidelines and to better understand how any draft price review processes would work in practice.

While helpful in a general sense of understanding the mechanics of the proposed approach to price reviews, the case studies outlined in the discussion paper demonstrate the excessive discretion provided to board staff in terms of how they will apply the guidelines and 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 be considered from the perspective of a Canadian or global rare disease innovator evaluating when and whether to bring a new patented rare disease treatment to Canada.

With those preliminary remarks in mind, this submission will now address some of the proposals outlined in the discussion paper. The following sections address the questions posed in the discussion paper.

Overview of the Proposed Framework

Overall, RAREi is encouraged by the brevity and clarity of the proposed price review framework and the notion that the board staff's initial oversight be limited to an international price comparison (IPC) in order to determine if additional review might be called for. RAREi also appreciates that the board is proposing to rely almost exclusively on the four factors delineated in the *Patent Act* in assessing what might be an excessive price.

This reflects RAREi's consistent endorsement of a minimalist and balanced approach to price regulation that is coherent with the PMPRB's recently clarified mandate in the *Soliris* case[7] – to ensure that patentees are not abusing their rights by pricing products excessively during a period of market exclusivity. RAREi remain convinced that the PMPRB's role should be limited and grounded solely in its legislative and constitutional mandate – specifically – to prevent the *abuse* of market exclusivity, not the legitimate *use* of market exclusivity.

As indicated above, a pragmatic approach to national price review is particularly important for rare disease innovators, which, operate in a very challenging, highly competitive global market. Predictability in the context of a PMPRB review would increase Canada's attractiveness for new medicines that many Canadians with rare diseases badly need.

Initial Price Review of Patented Medicines

RAREi supports the 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, rather than moving ahead with a review after only one comparable price is available, RAREi proposes that no IPC should be conducted until list prices are available in at least five PMPRB11 countries and that at least one is Germany, Sweden or Japan.

Regarding the board's question about what would be the appropriate price level within the PMPRB11 to reference for IPC purposes, RAREi recommends that only products with Canadian list prices that are higher than what is charged in other PMPRB11 countries should be considered for in-depth reviews. It would be a stretch to argue reasonably that a Canadian price at or below the median of prices in comparable countries is excessive, particularly in light of the removal of the US and Switzerland from the basket. As such, any Canadian list price that is equivalent to or lower than what is being charged in any other PMPRB11 country should be considered compliant.

[7] Alexion Pharmaceuticals Inc. v. Canada (Attorney General), 2021 FCA 157 (CanLII), [2022] 1 FCR 153: https://canlii.ca/t/jh8cg.

Moreover, RAREi believes that not every product identified as having a list price higher than the prices in other PMPRB11 countries should be automatically referred for an in-depth review. As RAREi has contended in the past, where there is clear unmet need or in therapeutic areas where there is a public policy rationale to support it, higher list prices than what are available in the PMPRB 11 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 for a list price that may be higher than the highest price in the PMPRB11.

In addition, the guidelines should also address situations where the US is the only potential comparator country explicitly. This is the circumstance that many rare disease products are in and can expected to be in going forward.

Post-Initial Price Review of Patented Medicines

Annual validation of patented medicine prices in the years after launch should only be reviewed for consumer price index (CPI) changes. If the CPI for the medicine has not increased beyond a specified threshold, the price should be deemed to have remained within guidelines and therefore not subject to referral for in-depth review. No additional IPCs should be undertaken.

In addition, some flexibility must be exercised in assessing the appropriateness of list price adjustments in the face of volatile inflationary times. The PMPRB's 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.

Finally, RAREi disagrees with the board's assessment that the lack of transition measures in the updated regulations obligates the board apply the new guidelines to existing medicines (i.e., medicines that received marketing authorization before July 2022). Board staff already have very significant discretion on a wide range of issues regarding when and whether to recommend a medicine for a hearing. One obvious area where this discretion should be applied is in allowing medicines that were previously deemed compliant and within guidelines and on the market – most often subject to significant effective price-lowering mechanisms such as the pan-Canadian Pharmaceutical Alliance (pCPA) – should not be subject to new list price evaluations.

RAREi believes that imposing new pricing rules on existing medicines would lead to significant operational challenges and could result in supply disruptions. Therefore, the PMPRB should avoid reviews – including the application of the IPC – that would apply to existing medicines after new guidelines are published.

For products marketed prior to July 1, 2022 that were priced at or below the previously accepted non-excessive average price on that date, and which did not increase beyond CPI in the meantime, should be deemed compliant and not subject to referral for in-depth review as long that the list price remains within a CPI adjusted amount. Such an approach would avoid the need for the time-limited transitional provisions proposed in the discussion paper.

Special Provisions – Complaints

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.

In terms of the types of products that should be subject to a complaints-based process only, RAREi urges the board to consider whether products that have been subject to successful national negotiations through the pCPA on behalf of

public payers or which are subject to national, hospital or blood product group and public purchasing processes should be subject a price review at all. Those pricing mechanisms have proven successful in consistently securing high-value commercial arrangements on behalf of all Canadian jurisdictions, thereby limiting the necessity for PMPRB oversight.

Regarding the question of who should be allowed to lodge a complaint, RAREi believes that the right to do so should be limited to the minister of health or any of his/her provincial or territorial counterparts. They are the best positioned to assess whether a complaint is relevant to the board's limited mandate. 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.

In-Depth Review

RAREi endorses the PMPRB's proposed streamlined approach to conducting in-depth review, relying primarily on the factors outlined in the *Patent Act*. However, the members are concerned by the level of discretion being afforded to staff to determine if a board hearing should be recommended to the chair, particularly in terms of determining the appropriate therapeutic class comparators.

What is missing in the PMPRB proposals is a commitment by the board and staff to rely on dialogue and collaboration between the rights holder and board staff to address any differences regarding what would be a compliant list price. The proposal states only that "the Staff **may** (*emphasis added*) also hear comments from Rights Holders on a case-by-case basis." To RAREi, the 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 about the need for a hearing.

In RAREi's view, 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 would be a considered a "within guidelines" list price.

RAREi agrees that the PMPRB should continue to rely on voluntary compliance undertakings to address any concerns about list price excessiveness and only in the rare event of an inability to reach an agreement should any file be subject to a recommendation for a hearing.

Regarding therapeutic comparisons, RAREi agrees that they should only be undertaken as a fallback in exceptional cases. In those limited cases when therapeutic class comparisons are required, 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.

RAREi does not support the continuation of the Human Drug Advisory Panel (HDAP) in its current form as a resource to assist with scientific evaluations. RAREi members' experiences are that previous HDAPs have often identified questionable and/or inappropriate products as comparators resulting in highly problematic price points being deemed compliant. Those negative experiences have included the 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.

One significant issue is that the HDAP is comprised of individuals with specific areas of expertise that may or may not correspond with or relate to the therapeutic class(es) being considered. Still, 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.

In the event that a therapeutic class comparison is required, RAREi recommends that the comparator should be selected by a new panel comprised of independent, arms-length expert clinicians, and not by PMPRB staff. 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 determine what the appropriate comparator ought to be. RAREi believes also that those expert opinions should be binding on PMPRB staff and the board.

To clarify, such comparisons 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.

Conclusion and Recommendations

In light of the above, it is RAREi's position that PMPRB should remain focused on its core mandate and operate as a passive oversight agency that guards against an abuse of market exclusivity, which is a high bar, especially in the context of so many other price-moderating and value-generating initiatives across Canadian public and private payers. Given that focused mandate, and the broader policy goal of promoting and encouraging innovation, RAREi takes the view 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.

RAREi recommends that the new guidelines be developed in a manner that is consistent with the PMPRB's limited legislative and regulatory mandate and with broader government objectives related to the life sciences sector and rare disease policies in mind. Furthermore, guidelines should be designed to reduce uncertainty for rare disease developers.

It must be stressed that 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 PMPRB guidelines are not crafted carefully and in a way 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.

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, argenyx Canada, Biogen Canada, BioMarin Pharmaceutical (Canada), Boehringer Ingelheim Canada Ltd., GlaxoSmithKline Canada, Ipsen Biopharmaceuticals Canada, Johnson and Johnson Innovative Medicines Canada, Mitsubishi Tanabe Pharma Canada, Recordati Rare Diseases Canada, Sanofi Canada, Sobi Canada, Takeda Canada, Ultragenyx Pharmaceutical and Vertex Pharmaceuticals (Canada. For more information, please visit www.rarei.ca.