

August 4, 2020

Dear PMPRB Consultation Committee,

Several key stakeholders in the pediatric community have collaborated to provide our perspectives on the proposed Patented Medicines Pricing Review Board (PMPRB) Draft Guidelines, as published in June 2020. We understand that, since its inception, the mandate of PMPRB has been to “prevent pharmaceutical patentees from charging consumers excessive prices during the statutory monopoly period”. We acknowledge that Canada’s drug prices are one of the highest in the world¹ and that pricing control is essential to ensure we can continue to have a thriving healthcare system. In this regard, PMPRB has an important role to keep healthcare spending for medications at affordable levels for Canadian taxpayers. The Government of Canada has indicated that affordability, accessibility and appropriate use, are key objectives in providing healthcare to Canadians². Careful consideration is needed to weigh the lowest price for a medication against its accessibility and it is this careful equilibrium in pediatrics that we are concerned could become inadvertently unbalanced with some aspects of the new PMPRB reform that is proposed. We would like to ensure that medicines in pediatrics, as well as those used in rare diseases will continue to be available for Canadian children.

Before we delve into the specifics of the PMPRB reform that is proposed, we would like to highlight that regardless of the PMPRB reform underfoot, we feel that pediatrics does not fit within the framework that exists today, or the one that is proposed for tomorrow. We assert that **pediatric specific criteria should be developed at all levels** of the drug approval, market access and listing processes, including PMPRB, to ensure that Canadian children have access to the medications they need. The failure to do so will exacerbate the existing problematic situation in that Canadian children frequently either do not have access to medications that are available in other developed countries, or that pediatric medicines and formulations are never commercialized in Canada due to the market size and the complex regulatory, reimbursement and pricing systems. In this regard, through Health Canada’s regulatory modernization initiatives, as well as alignment efforts with HTA bodies, some progress has been made. Canada, however, continues to lag behind other countries, and certain aspects of the new PMPRB reform could further negatively impact a situation that is already threatening for children in Canada.

Canadian children deserve the same pharmaceutical standards, and treatment options as adults to guarantee that their quality of care is optimal. PMPRB has a role to ensure that this is maintained with its reform.

¹ https://www.canada.ca/en/health-canada/news/2017/05/backgrounder_improvingaffordabilityaccessibilityandappropriateus.html

² https://www.canada.ca/en/health-canada/news/2017/05/backgrounder_improvingaffordabilityaccessibilityandappropriateus.html



We support revisiting the comparator countries to ensure that they are fair and reasonable

We cannot state which countries are the best comparators, this should be left to expert stakeholders. We do agree that adjusting the basket of countries to use comparators that are more relevant could make a difference and could contribute, in some cases, to an equitable price. Our experience with pediatric formulations indicates that Australia is a solid comparator because they have a similar commonwealth-based healthcare system and size of population. However, it would be important to ensure that the comparators are justified for specific circumstances. For example, a new pediatric formulation, such as a liquid oral flavoured medication should be compared with the same formulation in these comparator countries and not the more-widely used adult form, if it exists.



Economics-based price regulation factors should have special pediatric considerations to ensure access and fairness

Pediatric medicines and formulations

In our view, there are several reasons why certain aspects of the PMPRB reform could negatively impact pediatric medications and clinical research more acutely than in other populations. Firstly, the Canadian market is only 2% of the global pharmaceutical market and the pediatric market only 10% of the Canadian market. Because of this, pharmaceutical companies are already challenged to make a business case to commercialize **pediatric** medicines in Canada, despite the availability of these medications on the market of other developed countries. Secondly, our regulatory, reimbursement and pricing environment is perceived as being **complex and unpredictable**, making pharmaceutical companies less inclined to pursue commercialization efforts in Canada. As an example, commercial forms of certain medications are often unavailable to Canadian children while suitable child-friendly formulations are commercialized in the US and/or Europe. When commercialization in Canada does not occur, health care providers must use the adult formulation and adapt it for use in children (called “compounding”) in order to provide them the therapies they needed. This manipulation is not without risk and may result in health care providers administering a suboptimal dose leading to lack of efficacy, or a higher dose, that may increase the risk of adverse drug reactions.



Recent data have shown that the number of New Active Substances launched in 2019 is significantly lower today than the global launch rate of New Active Substances. Many of those medicines launched in this period in Canada are in oncology or rare diseases³. As a gap in the ability to access pediatric medications and child-friendly formulations in Canada already exists, and is recognized by the pediatric community, we need to be mindful of how price controls could affect the access of these medications for Canadian children.

Rare diseases

The treatment of rare diseases is also of concern within certain aspects of this new framework as rare diseases are usually evaluated in a similar manner as other therapeutic classes. A large proportion of

³ IQVIA MIDAS® Database, all new launches within Jan 1, 2000 – Dec 31, 2019 (Data extracted on Mar 13, 2020). Top 25 countries based on 2019 sales. Austria and Sweden were excluded due to launch data quality. NAS: New active substance. Taken from Life Sciences Ontario Webinar, June 22, 2020.



rare diseases begin in childhood and are currently without treatment. New therapies are being developed that could significantly improve the quality of life of these patients as well as the course of their disease; however, these treatments are often expensive. Similar to what has been done in the United Kingdom, PMPRB needs to ensure that it has a framework that can evaluate these treatment options in a fair manner that accounts for these unique circumstances to **support a price that is reasonable for all**. One size cannot fit all in the evaluation of pricing of rare diseases.



We are concerned that Canadian children may not have access to cutting edge clinical trials or innovative therapies



Children are not mini-adults, and as such, we need clinical trials to produce data specifically for this population otherwise there is a danger that their pharmacotherapy needs are not appropriately met. In April, 2020, Rawson published data looking at two clinical trial databases from November 1, 2019–March 15, 2020 and compared the number of trials in Canada and the US. The results observed was there was a decrease of more than 52% compared with only 21% of clinical trials for the period⁴. One can imagine the negative impact when the adult form is not available to adapt for children. What are the options when even compounding is not a possibility? This creates a larger gap for children in our healthcare system.



The Canadian pediatric research community led by the Maternal Infant Child and Youth Research Network (MICYRN) is spearheading the streamlining of timely and efficient clinical trials in Canada to increase the number of trials and to leverage our robust research infrastructure. Their laudable mandate includes the mapping of pediatric clinical trial units across Canada, developing resource documents for clinical trial units, being a single point of contact for industry sponsor and academic research, working with Health Canada to develop a risk-based clinical trial procedure, cross-jurisdictional ethics harmonization and contracts processes for child health studies, and consolidating international relationships. Clinical trial starts were significantly reduced in recent years⁵. When pharmaceutical companies perform fewer clinical trials in Canada, this reduces investment in research from the private sector, which is an important source of funding for research in Canada. It may also be a sign that manufacturers do not intend to commercialize new medicines in Canada. This reduction in clinical trial activity would have a significant impact on our universities, teaching hospitals, and our ability to attract high profile researchers, employment and most importantly access to breakthrough therapies for children in Canada.

Aside from the usual pharmacovigilance that is required when a medication is approved, for pediatric medications and for those used in rare diseases, there is no requirement to collect the real-world

⁴<https://www.canadianhealthpolicy.com/products/clinical-trials-in-canada-decrease--a-sign-of-uncertainty-regarding-changes-to-the-pmprb-.html>

⁵ <https://www.canadianhealthpolicy.com/products/clinical-trials-in-canada-decrease--a-sign-of-uncertainty-regarding-changes-to-the-pmprb-.html>

data once the product is on the market. This could inform how effective and safe a new medicine is in a real-world setting, a few years after launch.

The advances made by MICRYN and the pediatric research community to simplify and lead clinical research in Canada could be negatively impacted if the PMPRB reform adopts prices that are so low that there is no commercial interest in Canada, and therefore lack of any interest in clinical trials and clinical investigation.

Solution: There is a need for harmonization and simplification of the review processes across the healthcare system for commercialization of pediatric medicines

A number of key stakeholders in the pediatric community recently published a policy paper entitled [Improving Paediatric Medications: A prescription for Canadian children and youth](#). In this paper, we provided recommendations to the Minister of Health to improve access to safe and effective medications to Canadian Children. Harmonization and streamlining the approval, reimbursement and pricing processes across the various agencies is essential. In the Policy Paper cited above, we recommended to establish and fund a permanent Expert Pediatric Advisory Board (EPAB) at the Health Portfolio level. Accountable to the Deputy Minister of Health, this Board would advise on regulatory, reimbursement, and pricing activities related to pediatric medications and therapeutics. The layering of additional processes to this framework, as is suggested by certain aspects of the new PMPRB reform, could further negatively impact Canada's ability to access pediatric medications and formulations.

We note that PMPRB's motto is "[Canada's drug price watchdog](#)" which is located at the top of the Consultation form. We believe that a collaborative approach, versus a policing approach (as reinforced in this motto), would be beneficial as other parts of the healthcare system are looking to increase efficiencies and decrease costs.

Solution: Pediatric specific criteria are needed when evaluating medications and formulations for pediatric use: Adult parameters may not be appropriate.

1. Using the appropriate comparators for pediatrics

In the June PMPRB Guidance document, the Scientific Review Process and Categories are broken into two parts: Evidence-based Process and Review. The Evidence-based process will determine the therapeutic criteria, **appropriate comparators** and comparable dosage regimen. The Review will be based on patentee submission, research by a drug information centre, research by staff and the PMPRB Human Drug Advisory Panel. Without specific pediatric expertise to evaluate the cost-benefit analysis (or cost-effectiveness threshold) against criteria that are suitable for children, errors could be made that would inhibit our ability to provide the same quality care to children as other Canadians. Moreover, the comparator used in pricing evaluations is critical in children as compounding is common practice, which presents a unique and distinct situation compared to adults. Due to the lack of pediatric medicines and formulations in Canada, healthcare providers are forced to compound the adult form which, compared to a commercial pediatric form is, generally, quite inexpensive. We have



encountered the situation where a commercially formulated medicine's cost benefit was not positive, as the comparator used was the compounded medication, which is simply not the appropriate comparator to use. One cannot compare the high-quality manufacturing standards and research required by Health Canada to an adaptation done of an adult drug on a, patient by patient, basis in the pharmacy or the patient's home.

2. Recognizing that adult indications and formulations are not therapeutically equivalent to those needed in pediatrics

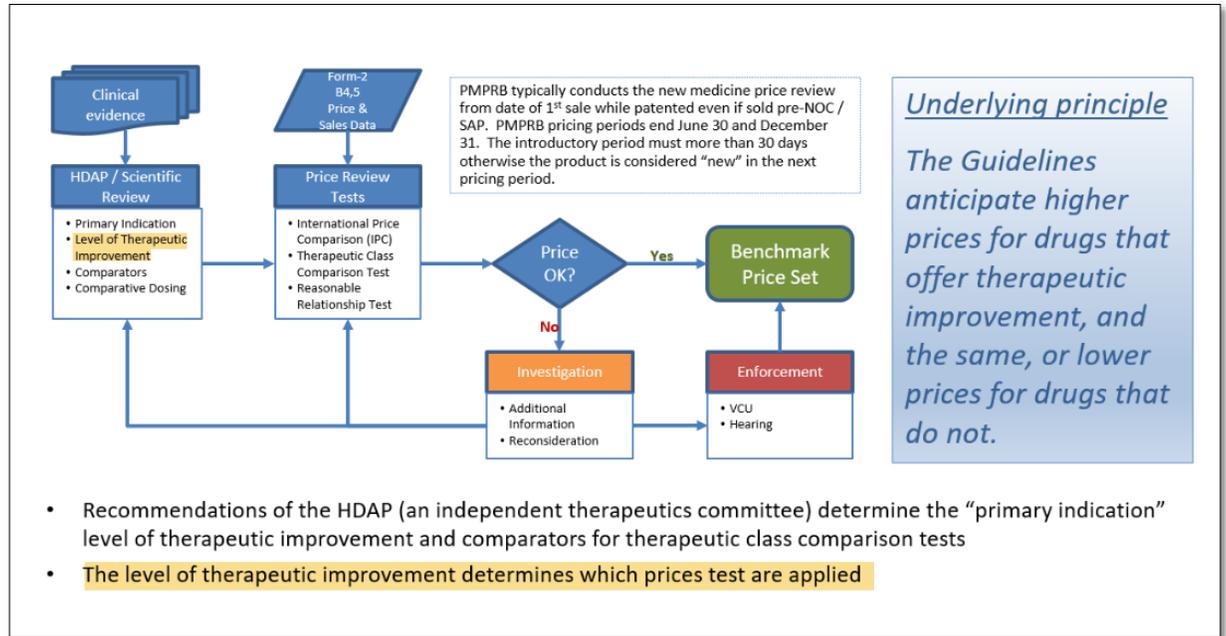
PMPRB will categorize medicines to determine which pricing tests will be applied. When the therapeutic value is not deemed to be incremental then a stricter pricing framework is applied. As we understand it, if a new medicine offers an easier administration of a marketed product then the PMPRB deems that the medicine may be classified as a "Therapeutic Criteria Level III"⁶. This suggests that it may not have incremental value and is considered equivalent with what exists on the market⁷. This will result in the application of the strictest pricing test that will have the lowest price ceiling possible (see Figure⁸ below, yellow highlight is ours). The comparators chosen by HDAP are typically based on approved indications and this may be a major issue for children, in whom therapy is frequently not based on the indications on the product monograph. This is a consequence of Canada not requiring pediatric trials for drugs likely to be used in children in contrast to the US and European experience, which may result in the choice of comparators inappropriate for children.

This application of a lowest price ceiling for new administrations or formulations in pediatrics is detrimental to Canada's children. In many cases, the adult forms are not suitable for administration in children because: the strength of dose needs adaptation; the form – e.g., pills cannot be used in young children; taste; excipients that are above the threshold of acceptable levels such as sucrose or alcohol, just to name a few concerns. In particular, taste can be crucial for adherence in children a factor that is less relevant in adults. Therefore, in pediatrics, new administrations and formulations **should not** be viewed automatically as being equivalent to existing administrations and formulations for adults. thereby demanding the lowest price ceiling. Pediatric expertise is needed to evaluate such equivalency tests on a case-by-case basis.

⁶ Therapeutic Criteria Level III The patented medicine provides moderate absolute improvement in therapeutic effect, relative to other medicines sold in Canada. The medicine may have (a) an increase in clinically relevant efficacy; (b) be associated with a reduction in the incidence or grade of important adverse reactions; or (c) be associated with clinically relevant increased ease of use characteristics (e.g. route of administration, convenience, increased compliance, etc.), however, these improvements may provide limited meaningful clinical impact or may be based on lower quality clinical evidence. Patented medicines at this level are normally associated with moderate incremental QALY gains with a relatively high degree of certainty or a high QALY gains with a relatively low degree of certainty. Taken from page 37 of <https://www.canada.ca/content/dam/pmprb-cepmb/documents/consultations/draft-guidelines/2020/PMPRB-Guidelines2020-en.pdf>

⁷ <https://www.macdonaldlaurier.ca/is-the-patented-medicine-prices-review-board-selling-canadians-a-lemon-nigel-lawson-for-inside-policy/>

⁸ PDCI June 2020 webinar slide 7.



3. Redefining the benefit of medicines for the pediatric population

In this new Guideline, the PMPRB Board staff are given additional powers during investigations, and our primary concern is without pediatric expertise, the Board staff may not appropriately value the benefit of a certain medication for the pediatric population. This is especially true in areas of rare or ultra-rare disease where there are few patients and there is a need for these unique therapies, where often there are no other options. A second concern that arises is that it would appear that the Board would be both the judge and the jury to adjudicate files, and without external evaluation, we feel that there may be a potential conflict of interest or a lack of objectivity in this review process.

In addition, it appears to us that the equation used to determine the Quality Adjusted Life Years (QALY) which is defined as life expectancy multiplied by quality of life utility should have pediatric specific parameters. The need for child-specific instruments to measure health-related Quality of Life has been demonstrated a number of times and we would argue that this is no different in the realm of pharmacoeconomics. Children have many years of potential life ahead of them and having them in school so they can become productive employable citizens is of utmost importance and should be included in this calculation. In terms of rare diseases, those medications which are curative, and likely more expensive, should be evaluated differently than those that are used for chronic treatments. These are examples of factors that should be included in the QALY calculation.

Additional benefits to the health system as a whole, may be needed to be considered in pediatrics by PMPRB. We understand that this may be a complex undertaking. In children it is not only the individual whose life is impacted by the disease but also the life of the parents or caregivers (ability to work, parent other children, etc). The price that society is willing to pay (direct and indirect costs) of a pediatric medication may therefore be different than in other areas.

Regarding Cost Effectiveness Thresholds (CET) we understand that the accuracy can be based on either a demand-side “willingness-to-pay” and a supply-side “opportunity cost”. The demand side of CET includes health spending determined by society’s preference and requires a flexible budget, whereas, the opportunity cost is based on how much a new intervention will displace an existing one and what is the impact of this displacement. Our understanding is that CET evaluations are mainly based on supply-side parameters as the demand-side parameters are much more difficult to quantify. We understand this may be difficult, however, in children, there could be many more demand-side factors that should be considered in the CET, even if they are a challenge to quantify. Again, this requires pediatric expertise as part of the decision making to ensure that these factors are considered.

Solution: Rare Diseases Require a Unique Framework

A rare disease is defined as a condition affecting less than one in 2000 people. However, with over 7000 rare diseases that collectively affect one in 12, or approximately 2.7 million Canadians and their families, collectively, they are not rare: around 75% of rare diseases have their onset in childhood and the large majority of affected children are currently without treatment. Rare diseases contribute disproportionately to mortality and morbidity rates, have an enormous negative impact on patient family wellbeing, and consume a disproportionate share of spending in health care, education and social support.

The “genomics revolution” has led to heightened awareness of rare diseases—80 % of which have a genetic basis. With causative genes being discovered at a remarkable rate, diagnosis and treatment are becoming more of a reality for patients and their families. With so few patients in one region, or even country, presenting specific rare diseases, it is also recognized that international collaboration is critical. The low number of patients in one country with a specific rare disease creates a significant obstacle to conducting clinical trials. Collaboration between the EU, US, UK, Australia, Japan and Canada are existing and will only grow with the development of master protocols, network and real world trials. There is a growing and accelerating pipeline of advanced therapeutic products for rare diseases and pediatric conditions which include biological, gene therapy, somatic cell therapy, tissue engineering with some of these therapies having the potential to be curative. It is important, almost ethical, that Canada’s children be offered the opportunity to be included in these clinical trials: Oftentimes, these patients do not have any other treatment options. Canada must remain attractive to Industry sponsors. We appreciate that PMPRB has to ensure that a fair commercial price is balanced against our healthcare budget, but **we assert that rare diseases cannot fit into the same pricing scheme as outlined in the guidance document.** Similar to what is outlined in United Kingdom’s National Institute for Health and Care Excellence (NICE) policy, they are using different cost-effectiveness thresholds under certain circumstances and this may be a model that could be adopted in Canada. As an example, NICE has unique thresholds for end-of-life medications, oncology and ultra-orphan and highly specialized therapeutics. Canada should follow suit in instituting a number of thresholds to account for some unique circumstances and to ensure children in Canada have access to the medications that they need.

Solution: We need post-marketing real-world data gathered by academic researchers

Within its reform, PMPRB should recommend to the Minister of Health, a framework that supports Canadian researchers financially to collect real-world evidence after drug commercialization. This would supplement data generated through clinical research with real-world efficacy and safety data, to better understand the therapeutic value of the new medication and inform clinicians in their decision-making process. This is true for every drug, but even more so for high costs drugs such as those for rare diseases and oncology. The data generated could be used to further inform PMPRB, and other agencies, of the cost benefit vs price of any new treatment.

Recommendations

- There is too much at stake to continue to move the rest of framework based on economic factors for January 2021. The impact on pediatrics needs to be better understood and added to the guidelines. We recommend that PMPRB continues to collaborate with major stakeholders and governments to simplify and clarify the pricing process.
- Any PMPRB reform must look at the impact to the health system as whole in pediatrics, which requires collaboration and harmonization. Given that PMPRB is one of the last steps in the drug approval and market access process, a failure to do so negatively affects any improvements upstream in the process.
- Rare diseases cannot fit within the same framework as other therapeutics. They require their own criteria and methods to evaluate the benefit to society.
- Establishment of an advisory committee including clinicians and patients (such as those that exist at CADTH and INESSS) that will provide expert pediatric input on all aspects of the “pricing determination” process. This will also help ensure transparency, accountability, and appropriate appeal.
- Clinical research has already declined since the PMPRB reform has begun and Canadian patients cannot afford not to have access to these innovative therapies. We need to maintain our robust pediatric clinical research infrastructure.
- Supporting the collection of real-world data of certain drug, for example, high cost drugs during the early years of marketing would allow the collection of safety and efficacy information to further inform the cost benefit of the treatment for the healthcare system.

Conclusion

The framework that PMPRB is using should be tailored for pediatric medicines and it is imperative that any floor price imposed would not hinder access to pediatric medications. We know that the PMPRB already considers the impact of its decisions on the broader health care system as part of the Health portfolio. We believe that careful attention to pediatrics would be important as there are initiatives underway at Health Canada to simplify the process and we feel it would be important that PMPRB ensure that parts of its reform does not hinder the progress already recently made. We therefore strongly recommend that pediatric expertise be present at all decision points to safe guard against this risk.

Thank you for your kind consideration in this matter. We are a group of national pediatric experts who are very willing to support PMPRB in its reform but it must be done at a pace where we can

understand the impact of these changes within the healthcare system. **We urge you to reconsider implementing this framework in January 2021. Although progress has been made since the initiation of the PMPRB reform, we feel there is more work for all of us to do before its implementation.**

We encourage you to contact any of the undersigned, at any time, to discuss our proposed recommendations. It would be our pleasure to work with PMPRB, or the Minister of Health, to find solutions that take into consideration the needs of Canadian children.

Respectfully yours,



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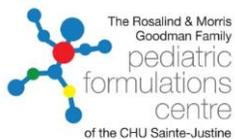


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