Submission on the June 2020 PMPRB Draft Guidelines
The Canadian Forum for Rare Disease Innovators (RAREi)
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1. Introduction

The Canadian Forum for Rare Disease Innovators (RAREi) appreciates the opportunity to offer feedback on the revised draft guidelines issued by the Patented Medicine Prices Review Board (PMPRB) in June 2020.

RAREi acknowledges the efforts made by the PMPRB to consider and address some concerns raised during the consultations related to the first draft guidelines circulated by the board in November 2019. However, RAREi members remain concerned that Canadian patients will be unable to access innovative treatments for rare diseases, given the continued uncertainty and unreasonableness of the mandated price controls.

As expressed in RAREi's previous submission, it is already very difficult to commercialize new rare disease treatments in Canada under the current pharmaceutical review system. Despite the proposed changes outlined by the PMPRB, the new price review regime would significantly exacerbate the challenges facing rare disease patients, innovators and health systems.

In particular, the proposed price reductions would represent a major deterrent to innovators contemplating bringing new medicines to Canada. Key concerns that remain include:

- The inappropriate use of economic factors to set market prices
- Substantial price uncertainty

- Lack of rewards in the new system to encourage innovation; rather the system punishes medicines that patients with rare disorders need to survive or improve their quality of life
- New reporting rules that could jeopardize compassionate access and patient support programs offered by patentees

It should be recognized as well that since the release of the November 2019 draft guidelines, everyone has been challenged by the COVID-19 pandemic. Fortunately, the innovative pharmaceutical industry – including many RAREi members – immediately rose to the challenge and undertook ambitious research and development activities on a global level in order to respond to the urgent need for treatments and vaccines to address the virus. However, the emergence of this virus and the likelihood of future threats of a similar nature, sharpen the need to support and encourage new medical innovation domestically and internationally. The looming impact of the new federal price controls, and the prospect that allowable prices may make it uneconomical to launch new products in this country makes it uncertain that new therapeutics and/or vaccines, even those developed domestically, would be made available here.

In addition, the recent Federal Court of Canada decision related to the revised *Patented Medicines Regulations* (PMRs) which authorizes the PMPRB's regulatory function requires the PMPRB to fundamentally rework its proposed guidelines. The Federal Court found that a key element of the new regime – the requirements related to patentees' reporting of third-party discounts and the new price calculation that determines the maximum rebated price (MRP) – is outside the scope of the *Patent Act*, and therefore, invalid.[1] The enforcement of the PMPRB's proposed MRP framework is dependent on the board's ability to collect and assess such information from patentees and, therefore, the guidelines must be modified substantially. Given that, RAREi questions the feasibility of continuing the current consultations and proposes that the PMPRB develop and consult on guidelines that account for its mandate that is limited to examining the ex-factory prices of patented medicines.

Please note that this submission is intended to be complementary to the input provide by Innovative Medicines Canada and BIOTECanada.

In the context of the above, please see some more specific input on the proposed regulations below.

2. Impact of the proposed new price controls on access to orphan treatments

RAREi was disappointed to discover that despite its request that appropriate accommodations be made within the new price review regime to properly recognize the unique characteristics of rare disease treatments – and provide incentives for their commercialization and development in Canada similar to those found in other jurisdictions – the PMPRB opted instead to remove any considerations for orphan treatments from the guidelines.

While RAREi appreciates the fact that patented medicines that achieve less than $12 million in sales would be regulated based only on an acceptable maximum list price (MLP), the onerous and punitive approach to further regulating category one medicines would discourage most rare disease innovators with transformative medicines from considering the Canadian market as a desirable launch country. This

[1] Federal Court of Canada Decision, Innovative Medicines Canada v. Canada (Attorney General), June 29, 2020: https://decisions.fct-cf.gc.ca/fc-cf/decisions/en/item/481803/index.do.

will mean that patients and their caregivers will be denied access to important treatment options that may represent their best hope for relief from the conditions with which they are faced.

Under the currently-proposed guidelines, MLPs for most patented medicines can be expected to decline by approximately 15% lower than current list prices as a result of the changes to the basket of countries and the move to the international median across the 36 Organization for Economic Co-operation and Development countries (despite the fact that Canada is a top-10 global economy). However, the subsequent provisions designed to achieve a compliant MRP would require innovators to consider additional price reductions amounting to as much as 80% below the MLP.

Such severe price reductions, to say nothing about the administrative and cost burden of complying with the PMPRB's complicated new price review regime (which has become more complex and uncertain with each new version of the guidelines), would represent a major deterrent to innovators contemplating bringing new medicines to Canada. They would be particularly onerous for RAREi members, which are primarily small and medium-sized companies dedicated to addressing the needs of rare disease patients.

To clarify, RAREi members actively negotiate price concessions and outcomes-based agreements with payers around the world to address affordability and sustainability concerns. However, if the cost of market entry is a drastic upfront price cut that puts Canada offside the rest of the global market, it is unlikely that this country would be prioritized within the global launch sequence, indicating, at a minimum, long delays for access to important new therapies, many of which offer the only treatment alternative for desperate patients and families.

As noted in RAREi's previous submission, if Canada becomes a late-tier launch country globally as a result of the new price controls, it also would 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 would be challenged to maintain their presence in this country.

There is plenty of recent evidence to illustrate this challenge, and the impact that the new price controls are already having on the market here in Canada including a recent *Inside Policy* commentary by Dr. Nigel Rawson. It summarizes much of the recent evidence well and demonstrates that the PMPRB is pursuing an aggressive pharmaceutical price cutting agenda using untried methods as it seeks a new way to regulate the industry.[2]

In addition, a literature review of studies examining the link between pharmaceutical pricing, research and development (R&D) and access to medicines published in the *Canadian Health Policy* journal found that 90% of articles reviewed showed a significant negative relationship between pharmaceutical price controls and investment in pharmaceutical R&D or access to innovative medicines. The review considered all relevant published material between 1995 and 2020. It concluded that the claim made by

[2] Rawson N, *The Patented Medicine Prices Review Board Is Selling Canadians A Lemon*, Inside Policy, MacDonald-Laurier Institute, July 8, 2020: https://www.macdonaldlaurier.ca/is-the-patented-medicine-prices-review-board-selling-canadians-a-lemon-nigel-rawson-for-inside-pol

the Canadian government that there is no link between price and R&D or access to medicines is not supported by the evidence from the scientific literature.[3]

3. Assessing the revised draft guidelines against RAREi's previous input

In its submission addressing the November 2019 version of draft guidelines, RAREi identified a number of problematic issues. While some alterations were made in the revised draft, many of the most concerning aspects remain unresolved.

Inappropriate use of economic factors to set market prices

RAREi members have fundamental concerns about PMPRB's proposed reliance on incremental cost utility ratios (ICURs) as a price-setting tool. The nature of the ICUR calculation is inherently subjective and highly variable depending on the assumptions used. Since small alterations in underlying assumptions could have substantial effects on the resulting ICURs, they represent a wholly inappropriate way to establish a market price. For this reason alone, they should be abandoned by the PMPRB as a means of determining an acceptable MRP.

RAREi recognizes that consideration of pharmacoeconomic (PE) factors are now a required element of the PMRs, and therefore must be addressed by the PMPRB in its price reviews. However, the regulations do not specify how they should be relied upon, and it is notable that the longstanding consumer price index factor that must be considered is typically not referenced in price reviews, investigations or board hearings. In other words, the PMPRB has discretion on *how* it will use the factors and is not obligated to apply each factor in every case. In fact, given the recent judicial review decision referenced above, it is unlikely that the market size factor and the pharmacoeconomic factor can be operationalized as proposed in the updated guidelines. RAREi strongly suggests going back to the drawing board to consider whether to use these factors whatsoever, given they are the issues that have caused more uncertainty than anything in the PMPRB's guidelines modernization initiative.

At the very least, if PMPRB retains its plans to use ICURs in the context of setting an allowable MRP, then care must be taken to address RARE's previously articulated concerns about its reliance on reinterpretations of ICURs submitted by innovators to the Canadian Agency for Drugs and Technologies in Health (CADTH). A recent analysis conducted by Patient Access Solutions (see more on this review below) indicated that that the majority of CADTH's re-analyses result in ICURs that are 2- to 4-fold higher than those submitted to CADTH by manufacturers. Significantly, these recalculated ICURs are not subject to correction, oversight or validation by anyone outside of CADTH's review process and they may not reflect clinical realities or current medical practice. More importantly, PMPRB's intention to reduce ICURs for multiple indications, and widely-varying ranges for a given medicine to a single point estimate for all Canadian markets is simply unreasonable. These significant limitations must be addressed before the process is finalized.

Also, the proposed automatic additional 50% reduction in price for any category one high-cost medicine where no pharmacoeconomic assessment is available or was inconclusive is highly punitive and arbitrary. RAREi members are particularly concerned with this provision since it is medicines for small

[3] Labrie Y, *Evidence that regulating pharmaceutical prices negatively affects R&D and access to new medicines*, Canadian Health Policy, Canadian Health Policy Institute, June 2020: https://www.canadianhealthpolicy.com/products/evidence-that-regulating-pharmaceutical-prices-negatively-affects-r-d-and-access-to-new-medicines-.html.

populations which are most likely to be caught up in this scenario. It should be noted that this is precisely the kind of circumstance that drives the demand for a distinct health technology assessment approach for orphan treatments which recognizes the limitations of traditional PE methods to properly assess comparative cost-effectiveness of these therapies. Penalizing such medicines by arbitrarily forcing prices down by 50% plus is a recipe for closing the market to them.

Furthermore, while the proposed ICUR thresholds used by PMPRB to determine the additional price reductions required for "high-cost" medications have been increased, it is unclear how those new levels were established. No explanation is included in the backgrounder accompanying the draft guidelines regarding how the new thresholds were determined or what is the rationale supporting them. This suggests that the proposed threshold levels are arbitrary and without real foundation.

In fact, the backgrounder seems to suggest that the PMPRB recognizes the limitations of relying on ICURs as a mechanism for price setting. In the context of explaining its reliance on PE value to drive additional price reductions, it states "until such time as there is more developed empirical evidence in Canada on opportunity cost in the public health system, an argument exists for erring in favour of more generous thresholds that are aligned with the higher end of what is seen internationally and that provide greater certainty and predictability for patentees." This is a clear acknowledgement of the substantial risks associated with applying the PE factor. Proceeding on the basis of what are acknowledged by the board to be arbitrary threshold levels leaves open the possibility that the thresholds could be reduced at any time, leading to more restrictive price controls at some point in the future. Given the lack of clear evidence of a reliable means of assessing opportunity cost, RAREi believes the PMPRB should take a highly cautious approach when considering PE value in its price review process and refrain from or at least further restrict the use of such factors.

As part of it justification for their use, the backgrounder also refers to other countries' use of PE value thresholds in the review and approval of new medicines. However, it must be stressed that in those cases, PE value is relied upon in the context of health technology assessments or product negotiations, not for establishing strict price ceilings that are effectively a condition for market entry. In sum, the use of PE value thresholds to help set market prices creates enormous price uncertainty and would pose a significant barrier to product commercialization of innovative treatments in Canada at the expense of patients.

In addition, and as stated previously, price adjustments based on market size is an inappropriate and highly punitive regulatory measure which fundamentally discourages innovation, effectively regulating revenues as opposed to price. While the adjustment thresholds have changed significantly in the updated version of the guidelines, the ceiling lowering mechanism remains unreasonably punitive.

Price uncertainty remains

RAREi acknowledges PMPRB's introduction of pricing floors in the context of the calculation of the MRP. This was a positive development, which had the potential to eliminate some of the unpredictability associated with determining what might be the ultimate price ceiling for a given new medication.

Unfortunately, the proposed floors include a "trap door" that leads to even lower regulated prices when one considers the successive price adjustments required when a medicine achieves annual sales of more than $50 million. Medicines could face further regulated price decreases in the context of reassessments, which the PMPRB staff has overly-broad discretion to undertake.

The potential addition of the market size adjustments and category reclassification because of a reassessment makes it impossible for an innovator to determine in advance what the ultimate allowable price could be and the potential market size in Canada, which is a key determinant of the industry's ability to negotiate valuable financial considerations with payers, including the pan-Canadian Pharmaceutical Alliance.

Lack of rewards to encourage innovation

RAREi was pleased to see that medicines offering differing levels of inventiveness would be treated distinctly in the new draft guidelines. In particular, RAREi appreciates that the price floors are differentiated based on the relative level of therapeutic improvement a given medication demonstrates compared with other treatment alternatives. RAREi members continue to believe it is important that the PMPRB's pricing framework recognizes advances in innovation by rewarding innovators for progress made in addressing medical needs.

However, concerns remain with respect to the implementation of the policy.

First, the price floor percentages would still facilitate punitively low regulated prices (between 20% and 50% below the MLP) and appear arbitrary as they are not justified based on any objective standard. RAREi would prefer to see the potential reductions revised significantly to provide for more reasonable floors.

In addition, RAREi feels it is inappropriate for PMPRB staff, who have limited clinical expertise and inherent bias, to be relied upon to pass judgement on relative levels of therapeutic improvement among competing medicines. That is a responsibility that should be left to independent arms-length clinical experts to determine and for the board staff to follow.

The body that is called upon to assess the relative inventiveness of new treatment options must recognize and account for the particular challenges faced by rare disease innovators in generating traditional types of clinical evidence to support their new medicines. Conducting lengthy randomized control trials in large numbers of patients is often impossible for rare disorders. Despite this reality however, the lack of such data often results in the Human Drug Advisory Committee (HDAP) categorizing new rare disease treatments as nominally innovative. Those findings, despite innovators' reliance on scientifically credible alternative clinical trial designs discourages important rare disease therapies from coming to Canada. There is a need to allow for evaluators to assess such medications on the basis of a "promise of value" which could be proven through real-world evidence. That would allow for more appropriate and reasonable price ceilings for many of these transformative medicines.

New reporting rules could jeopardize patient access programs

RAREi notes that the revised draft guidelines do not address a key issue it identified in its earlier submission. Given that the regulatory amendments would require patentees to report price and revenue information net of all price adjustments, including direct and indirect discounts, it was assumed that the PMPRB would treat all treatments provided via compassionate access programs, including patient support programs, as zero dollar sales for the purposes of calculating the MLP and the MRP.

RAREi pointed out this would have a direct deflationary impact on allowable prices, which would discourage manufacturers from providing patients with complementary coverage through any mechanism, which would not be good for anybody. RAREi continues to explicitly encourage the PMPRB to maintain a free goods policy that would reduce the risk of discouraging manufacturers from offering free goods to patients on a compassionate basis or for supplying medicines for clinical trials.

The PAS analysis attached concurs, noting that several unique Canadian mechanisms of providing value to payers that, in turn, provide additional value to patients could be lost. Rare disease innovators currently invest in patient support programs, early access programs, and registries to ensure that patients are supported, they are provided access to treatments immediately after Health Canada approval and outcomes will continue to be measured to ensure that the medications are providing value in the very long term. These programs may be scaled back in the search for solutions to highly restrictive price limits.

4. Comments on PMPRB's EDRD analysis

RAREi notes that the PMPRB research unit has been recruited to support the board's perspectives on the proposed new price review regime by undertaking analyses that appear designed to offset or rebut common stakeholder criticisms of its approach. As a preliminary comment, RAREi is concerned that the PMPRB's communications do not meet the expected standards of a regulator to be objective, impartial, consistent and without conflict of interest or bias.[4]

Of particular concern, the PMPRB's recent research webinar addressing "expensive drugs for rare diseases" (EDRDs) appeared to be an overt attempt to offset stakeholder contentions that rare disease treatments deserve special consideration and accommodation in the Canadian medication review and approval process in order to ensure access. As RAREi stated previously, the very characterization of rare disease treatments as EDRDs is pejorative and reflects a lack of appreciation for the important impact that such medicines have on patient lives.

In response to the PMPRB analysis, RAREi contracted Patient Access Solutions Inc. (PAS) to review the board's material and prepare an evidence-based response. A copy of the full PAS report is attached to this submission as an appendix.

In summary, PAS found that the PMPRB's clear intent was to demonstrate that rare disease treatment costs are rapidly increasing in Canada. That apparent bias was reflected in key takeaways from the report such as:

- "Orphan medicines are increasingly dominating the new drug landscape…"
- "EDRDs *[are]* the fastest growing market segment, pushing the limits of affordability"
- "…most offer limited or unclear therapeutic benefit
- "…not cost-effective at their list price"
- "EDRD spending in Canada is above the OECD norm"

PAS expressed concerns that the PMPRB's EDRD research was presented in a manner that may cause readers to believe that rare disease treatments are not desirable and do not present good value for Canadians, including:

[4] These principles and standards are elaborated more fully in the OECD's 2021 Recommendation of the Council on Regulatory Policy and Governance (https://www.oecd.org/gov/regulatory-policy/49990817.pdf).

- The language used in the report was one-sided and did not appear to make any effort to put the findings into context. In particular, PAS noted that the PMPRB analysis did not comment on the innovation gains being made by new orphan medicines, the documented patient and caregiver perceptions about the truly life changing or life extending value represented by many of these new treatments or the fact that some recent rare diseases innovations have offered important incremental health gains to Canadian patients.
- The PMPRB's report did not address the fact that actual prices paid are much lower than the list prices due to nationally negotiated confidential agreements between payers and innovators.
- There was also no mention about the savings to the health system and society resulting from patients use of effective new treatments or the relative levels of expenditure on treating rare disease patients versus other investments that society is willing to make.
- The PMPRB analysis also did not consider the cost of rare disease treatments in the context of other health care expenditures or the impact on medication costs of other market segments.
- PAS also pointed out that most rare disease treatments are considered by Health Canada through its priority review mechanisms which are in place to ensure faster availability of new treatments for patients when there is a lack of available alternatives. By definition, medicines reviewed under the priority review process are those "*intended for the treatment, prevention, or diagnosis of serious, life threatening or severely debilitating illnesses or conditions."*[5] It indicated too, that there is wide discrepancy between the PMPRB's HDAP comparative value assessments compared with those produced by Health Canada and health technology assessment reviewers in Canada.
- The PMPRB analysis did not explain the drivers for its assertion that rare disease treatments appear to have unclear therapeutic benefit.
- Important context for the lay public would clarify that trials are small because it is challenging to find sufficient numbers of patients to enroll in the trials due to the rarity of the conditions and that trials often lack comparator arms because there is no clear standard of care to compare with or because available treatment alternatives may make the condition worse.

In an effort to balance the PMPRB analysis, PAS re-analyzed the data. In doing so it determined that the PMPRB analysis was highly skewed by the inclusion of oncology medications with non-rare indications. It argued that oncology treatments should not be included because they often receive subsequent approvals for additional indications for more common cancers that drive up their total expenditure. In addition, the prevalence of cancers typically increases over time while rare diseases are genetic aberrations and rates of inheritance are more stable over time.

PAS found that 48 of the PMPRB's list of 93 EDRDs were oncology medicines and two more were combination therapies that included molecules that were included as monotherapies as well. Nine were medicines that should not be considered as rare disease treatments and half had received, or could be expected to receive, Health Canada approvals for additional indications that would ensure that their use would exceed the incidence rates that would be considered rare. Only 14 of the 48 were considered actual treatments for rare disorders. This suggests that the PMPRB estimates of the proportion of total Canadian medication spending attributable to rare disease treatments was exaggerated.

[5] Health Canada, *Priority Review of Drug Submissions* Fact Sheet: https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/prfs_tpfd-eng.pdf.

In fact, the PAS re-analysis indicated that the majority of the EDRD cost growth reported by PMPRB is driven by oncology treatments. The compound annual growth rate for non-oncology orphan medicines is substantially lower (10%) than what the PMPRB presented for the full basket of 93 medicines its reviewed.

In addition, Canada's expenditure on rare disease treatments appears to be at, or below, the international norm when considering non-oncology orphan treatments only.

To prove the case further, research conducted by PAS and presented at the 2019 International Society for Pharmacoeconomics and Outcomes Research (ISPOR) meeting in Copenhagen demonstrated that the total annual Canadian public payer expenditure on non-oncology rare disease treatments 2019 was $280 million, representing just 2% of the national medication spending.[6] This figure is similar to the amount (2.5%) reported by the PMPRB for 2019 for private and public payers combined. That analysis concluded that the annual public cost of rare disease treatments is exceedingly small when compared with other benchmarks of public government and private/societal non-essential health spending.

5. Concluding remarks

As noted above, despite the PMPRB's efforts to address certain elements of the commentary received in response to its first draft guidelines, the changes proposed are not sufficient to address the fundamental concerns expressed by RAREi and a broad range of other stakeholders. And while it may be easy for the PMPRB to dismiss industry criticism, it must be stressed that the negative feedback received was widespread among the vast majority of patient groups which provided input, as well as many clinicians, pharmacists, distributors and voices from the life sciences and research communities.

At their heart, the proposed reforms appear intended to move the PMPRB away from its traditional role as a monitor against potential price gouging by patentees. Instead the regulations appear to establish a punitive set of national pharmaceutical price controls that will prevent or at least delay the entry of new medicines into the Canadian market. In most other jurisdictions and in Canada currently, favourable commercial terms are regularly negotiated between payers and pharmaceutical developers. Many individual patients benefit from compassionate and subsidized access to medicines provided by companies. Forcing maximum prices down as a requirement for Canadian sales undermines the capacity for the sector to negotiate or provide life-saving therapies through patient support programs and compassionate use.

The reliance on questionable new economic factors to drive prices down to levels well below what was initially proposed by Health Canada is very problematic both in concept and implementation. In addition, the inability for a patentee to establish a definitive price for a given product over time creates a level of uncertainty that makes entering the Canadian market a risky proposition with untenable implications for sales in other global markets. And beyond all of that, the impact of the proposed changes on rare disease treatments specifically, most of which will be subject to the most punitive elements of the proposed regime, suggest that the prospects for most orphan patients will be dashed, even in the face of unprecedented innovation that has lately offered real hope for survival and a better quality of life.

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[6] 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.

RAREi urges the PMPRB to work with the federal government to ensure that Canadians' values about the need to provide universal health care coverage are supported in regulations and practices in order to ensure that Canadians rare disease patients are not further disadvantaged compared with the rest of our society or citizens of other countries. Canada must find a way to ensure Canadians benefit from rare disease treatments. Failure to do so will result in unnecessary deaths, permanent disability, poor quality of life and substantial consumption of health care resources.

Rather than the onerous and regressive system proposed by the PMPRB, a more promising approach to regulating patented medicine prices would be to design a new price monitoring regime from the ground up, working with stakeholders to ensure that it is fit for purpose and works within the Canadian health care system. In fact, a more progressive and collaborative approach would position provincial health systems, patients and our vibrant medical research ecosystem for economic and health system recovery, and ultimately benefit the millions of Canadians affected by rare diseases, who rely on RAREi members to develop and deliver diagnostics and therapeutics to live and improve their quality of life.

APPENDIX

Report on the Unacceptability of the Proposed PMPRB Guidelines: Lack of Compatibility of the Guidelines with the Perspective of Patients and Caregivers and the Future of New Market Entry of Drugs for Rare Disease in Canada

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1. INTRODUCTION

The proposed Patented Medicine Prices Review Board (PMPRB) Guidelines released on June 20, 2020 and distributed for public consultation until August 4, 2020 appear to put undue downward pressure on the price of the drugs for rare diseases (DRDs) in Canada. This downward pressure exists even though DRDs offer the greatest level of innovation and/or target the highest unmet medical needs in Canada. Not only are the guidelines aggressively aimed at reducing medication prices in Canada that are out of step with other Organisation for Economic Co-operation and Development (OECD) countries, the guidelines for DRD price review are inexplicably misaligned with the pricing controls proposed for all other medications in Canada. The rationale for this misalignment appears to be cited in the PMPRB report entitled "*Insight into the spending on expensive drugs for rare diseases*". However, much of the analysis presented in the report has flawed logic and/or presents a single interpretation of the data that does not remotely take into consideration the patients' and caregivers' perspective on the value of, and need for DRDs. The report (and the proposed guidelines) also do not reflect on the potential risks to Canadian rare disease treatment manufacturers that would likely reduce the incentive of launching these new medications in Canada as the Canadian market would be highly unattractive to global-based decision makers.

This report provides an alternative viewpoint to the PMPRB analysis. The alternative must be considered when revising the guidelines to address the inevitable inequity in pricing of DRDs and to mitigate the risk of Canadian patients losing access to these novel drugs in the future.

2. OVERVIEW OF THE APPARENT BIAS HIGHLIGHTED IN THE REPORT ON DRD SPENDING

The stated objective of the PMPRB's EDRD research report (i.e., "*This presentation discusses the fast emerging market for [expensive drugs for rare diseases] EDRDs, from insights into how the development phase leads to the launching of orphan drugs, which combined with high-drug prices makes the EDRDs the fastest growing market segment, pushing the limits of affordability*") quite clearly expresses the intent to demonstrate rapidly increasing costs of DRDs in Canada. In addition to the apparent bias shown in the objective statement described above, the research methods employed do not appear to have been developed in a balanced manner. The researchers did not seek a multi-stakeholder view to examine the need for DRDs in Canada relative to other countries, the determinants of DRD pricing as it relates to market size versus development costs, or the appetite of Canadian citizens for funding of DRDs that would help fellow Canadians who are afflicted with devastating health conditions that can arise through the inheritance of genetic abnormalities.

The apparent bias is reflected by the Key Takeaways outlined in the report, which state:

- "Orphan medicines are increasingly dominating the new drug landscape…"
- "EDRDs *[are]* the fastest growing market segment, pushing the limits of affordability"
- "…most offer limited or unclear therapeutic benefit
- "…not cost-effective at their list price"
- "EDRD spending in Canada is above the OECD norm"

The language is one-sided and does not appear to make any effort to put the results into context with the challenges faced in the development of DRDs, the increasing costs of other drug segments, or the total cost of DRDs relative to other areas of healthcare spending for non-rare conditions.

3. PRESENTATION OF AN ALTERNATE VIEW OF THE RESEARCH DATA THAT COULD INFORM A TRULY BALANCED APPROACH TO A REASONABLE METHOD OF SETTING AND REVIEWING DRD PRICES

As noted in Section 2, the PMPRB's EDRD research is presented in a manner that may cause readers who are not involved in the pricing and reimbursement of pharmaceuticals on a daily basis to believe that DRDs are not desirable and do not present good value for Canadians.

For each of the Key Findings of the report, additional, balanced perspective should be presented to ensure that decision-makers and the lay public are fully informed. The additional perspective is provided below.

3.1 Additional perspective required to interpret "Orphan medicines are dominating the landscape"

In an evaluation of trends in a marketplace, a balanced assessment would look at the reasons for the observation, the pros and cons of the situation and would provide a conclusion addressing whether the current trend should continue. All these aspects are missing from the DRD growth data presented in the report. The researchers have offered a one-sided view that growth of the DRD market is not desirable. The report does not comment on:

- The gains in innovation being made (i.e., the fact that so many new drugs coming to market are targeting conditions that were previously untreatable or could only be treated in a symptomatic manner rather than treating the underlying causes of the disease).
- The documented patient and caregiver perception of the value of the drugs as truly life changing or life extending as outlined in patient/caregiver inputs to the health technology assessment (HTA) review processes conducted by the Canadian Agency for Drugs and Technologies in Health (CADTH) and the Institut national d'excellence en santé et services sociaux (INESSS).
- The fact that DRDs may be bringing the greatest incremental health gains to Canadian patients when compared with medicines for larger populations that were introduced into the market during the same period.

3.2 Additional perspective required to interpret "…pushing the limits of affordability"

Context was missing with regards to the presented conclusion which suggested that the costs of DRDs and targeted cancer drugs are unaffordable. Further context regarding the following statements is needed:

- Slide 10 indicates that the DRD market in 2019 only accounted for 2.5% of total pharmaceutical spending in Canada. The "limits of affordability" appear to be driven primarily by increases in the introduction of new cancer medications. By including cancer medications in a DRD affordability assessment, the relatively low-cost growth of non-oncology DRDs is obscured. Further information on the reasons why cancer medications should not be included in an assessment of DRD costs is presented in Section 4.
- The report does not reveal that private health benefits programs reimburse 40% or more of the total DRD costs.
- The report does not offer the important context that DRDs reimbursed publicly are subject to nationally negotiated product list agreements which provide significant discounts to the public health system. While specific discounts vary, they reflect values important to payers such as paying for responses, paying for wastage, ensuring market sizes aren't exceeded (by

implementing caps on utilization), etc. Thus, actual prices paid are much lower than the list prices due to the negotiated confidential agreements

- There is no information presented in the report that puts the cost of DRDs into context with other health care expenditures. For example, around 8% of Canadians have been diagnosed with a rare disease[1], while the annual costs associated to DRDs are estimated at 2.5% of total medication spending. This cost is a mere fraction of the public healthcare costs associated with smoking-related illness ($6.5B annually in Canada; Conference Board of Canada. Available here) and obesity (estimated to be $9B in Canada in 2021; Obesity Canada. Available here) and obesity (estimated to be $9B in Canada in 2021).[2,3]
- The report does not reflect on the contribution of medications toward patient health relative to the total costs of other healthcare expenses that are offset when effective drugs are available and individuals are able to go to school, enter or return to the workplace, and be productive members of society.

3.3 Additional perspective required to interpret "…limited or unclear therapeutic benefit"

By stating that DRDs have limited or unclear benefit, the report suggests to the lay public that the important benefits of the drug have not been acknowledged by Health Canada and have not been validated through the HTA review paths. A balanced research report should state the following:

- Most often, the DRDs are approved by Health Canada through its priority review mechanisms which are in place to ensure faster availability for patients who are diagnosed with diseases that lack treatment options. To suggest that these treatments provide only a moderate improvement compared with existing alternatives or, worse, little to no benefit is completely counter-intuitive and not consistent with the Health Canada priority review designations these products commonly receive.
- The report does not explain the drivers for the assertion that DRDs have unclear therapeutic benefit. Important context for the lay public would clarify that trials are small (i.e., because it is challenging to find a significant number of patients to enroll in clinical trials due to the rarity of the conditions), and trials often lack comparator arms (i.e., because there is no clear standard of care or because available treatment alternatives may make the condition worse).
- The report does not reveal that reports addressing the therapeutic designation of medicines reviewed by the PMPRB's Human Drug Advisory Committee (HDAP) are seldom made public and there are limited avenues for appeal when manufacturers, physicians, and patients disagree with those assessments. There is wide discrepancy between HDAP's comparative value assessments compared with those produced by Health Canada, CADTH and INESSS reviewers. Given the complexities involved, it is challenging for the lay public to appreciate why the PMPRB's therapeutic value assessments are often very different from that of other important review agencies that ultimately determine the marketability and the reimburse-ability of new treatments.

3.4 Additional perspective required to interpret "…spending…is above the OECD norm"

When comparing international spending trends, it is important to note that:

- Canada's expenditure on DRDs appears to be at or below the norm when considering orphan treatments only (i.e., excluding cancer drugs), and
- Total expenditure on DRDs in Canada is moderate even though prices tend to be higher, and
- Canada has a more heterogeneous population compared with some of the countries that rank lower than Canada in terms of DRD spending. In addition, context regarding the heredity of rare disease is required to assist readers to understand the difference between populations. From the data presented, it is not possible to assess whether the current expenditure is in line with the proportion of Canada's population that is afflicted and where treatments are more commonly required.

3.5 Additional reporting that requires clarification or further context for readers

- Slide 7 of the report suggests that DRDs are more likely to be approved (or have higher approval rates that non-DRDs). While this is true in earlier stage development, after they get to Phase 3 trials, DRDs and non-DRDs have very similar approval rates (i.e., DRDs are approved only 1.2 times as frequently as non-DRDs). The report does not seek to understand if the differing rates of approval are statistically significant and, if they are higher, why that is the case. It is possible that approval rates are higher because there is unmet medical need? Moreover, if the approval rates are higher, this contradicts the statement on Slide 14 suggesting that "*most EDRDs offer limited or unclear therapeutic benefit*". If the DRDs have higher approval rates than non-DRDs, how can they also be more likely to have limited or unclear therapeutic benefit?
- Slide 8 suggests that there has been a total of 109 new drugs launched in the period from 2009 to 2019. However, the report indicated that 93 DRDs and targeted cancer drugs were launched. It is, therefore, assumed that the data reported on slide 8 includes additional indications approved for some of the 93 as is typical of many cancer drugs (see Section 4 for further information on the need to exclude cancer drugs from any analysis of the cost of DRDs).
- Slide 8 also shows in the bar graph that 51 new medicines were approved in 2019 in Canada; however, the pie chart shown on the same slide compares the annual cost of only 25 new medicines. It is unclear why 26 medicines were excluded from the pie chart. We acknowledge that it may just be a typo.
- Slide 10 shows that the majority of the EDRD cost growth reported is driven by oncology drugs and not non-oncology DRDs. The compound annual growth rate for DRDs is relatively low (10%).
- Slide 11 should present the OECD rankings for DRDs separate from oncology drugs as noted in Section 3.4. In addition, readers need to understand the contribution of biology (and medical need) to the spending versus the contribution of relative pricing across countries. Without context regarding the number or proportion of citizens with rare diseases or the relevant cancers, a presentation of the ranking of spend is meaningless.
- Slide 12 requires context regarding pricing relative to the number of patients that could potentially be eligible for treatment. Rarity affects price. Drugs approved for rarer conditions tend to be priced higher than those for larger populations. In addition, the analysis should remind reviewers that these prices reflect list prices only and not the net prices paid by drug plans.

- Slide 13 indicates that the Canadian cost of DRDs and targeted cancer drugs are more in line with international prices than those medications not classified as rare. In addition, the costs shown do not reflect the confidential rebates. We are confident that the Canadian prices would be more favourable in the global context if rebates were considered.
- Slide 14 should offer the important context that the incremental cost-effectiveness ratios (ICERs) used to inform CADTH's price reduction recommendations reflect the worst-case scenarios. CADTH's economic reviewers notoriously reassess manufacturer-provided economic evaluations using assumptions that increase the ICER to the greatest degree. Most Canadians do not understand pharmacoeconomics and would not have the knowledge to understand the subtleties involved in determining ICER values, and the wide variability in potential results that can come from minor alterations in the underlying assumptions utilized within the model. In addition, researchers in the UK and CADTH have indicated that a higher threshold is acceptable for DRDs; an ICER of $100,000 is too low.[4,5]
    - UK study: "*Using the NICE incremental cost-effectiveness threshold (£20K per QALY) as an anchor and adjusting by R&D costs and expected market revenue, in the base case scenario we estimated the adjusted reasonable CET for orphan drugs to be £39.3K per QALY at the orphan population cut-off and* ***£78.5K per QALY at the orphan population mid-point. For ultra-orphan drugs (with a patient population size of 1 in 50,000 or lower) the adjusted CET resulted in £938.4K.***"
    - CADTH: **"***Several modifications have been made in ICER's economic evaluation to address the unique need of DRD, such as producing a cost-effectiveness model for every new treatment; broadening the analysis for willingness-to-pay threshold results from $50,000 per QALY to* ***$500,000 per QALY****; highlighting in the report that decision-makers, nationally and internationally, may accept higher cost-effectiveness ratios (compared to other non-DRD) by giving additional weight to other benefits and considerations; inclusion of broader societal costs in its economic model when such costs are substantial; and, when necessary, conducting a search for "mapping" studies to help translate surrogate outcomes into quality of life measures*."
- Slide 16:
    - RAREi supports the federal government's promised investment of $500 million per year to support a national rare disease strategy. The PMPRB's proposed price review regime and its impact on DRD pricing limits is completely inconsistent with the government's pledge to invest in these needed medications.
    - It is unclear why the priority review mechanism is mentioned, but in any case, it would be important to note how many of the 93 drugs analyzed were reviewed through a priority review mechanism. Our analysis found that 51 of the 93 drugs were reviewed by Health Canada with a priority review designation.
    - In addition, as mentioned in Section 3.3, the existence of the priority review mechanism is contradictory to the point made in slide 14 regarding the lack of therapeutic value of a good portion of DRDs. By definition[6], "*Priority Review status may be granted to drug submissions intended for the treatment, prevention, or diagnosis of serious, life threatening or severely debilitating illnesses or conditions where*
        - *there is no existing drug on the Canadian market with the same profile or*

- *where the new product represents a significant improvement in the benefit/risk profile over existing products.*

4. ANALYSIS OF THE CONTRIBUTION OF NON-RARE ONCOLOGY DRUGS TO THE TOTAL "EDRD" COSTS

4.1 Introduction

RAREi is firmly of the opinion that targeted oncology drugs should not be included in any analysis of the cost of DRDs. The total increasing cost of DRDs is skewed higher by their inclusion and obscures the reality that spending on DRDs in Canada is relatively low. Cancer drugs should be excluded from determinations of appropriate pricing for DRDs for the following reasons:

- Oncology drugs often receive subsequent approvals for additional indications. Frequently, the subsequent indications address much more common cancers that drive up the total expenditure.
- Canada has an existing mechanism that ensures fair pricing for new cancer medicines through a national system of negotiated rebates/confidential prices which requires each new indication to undergo a new price negotiation that gives all public payers across Canada an opportunity to ensure the confidential price reflects the value and the market size of the new indication.
- Cancer medications are generally provided for a more limited duration of time compared with DRDs for orphan indications which, in most cases, are provided to patients lifelong.
- CADTH has recognized the differences between oncology and non-oncology drugs and reviews them through different pathways.
- The prevalence of cancers typically increases over time while rare diseases are genetic aberrations and rates of inheritance are more stable over time.

Patient Access Solutions' (PAS) examination of the PMPRB's "*Insight into the spending on expensive drugs for rare* diseases*"* report determined that the PMPRB EDRD cost analysis may have been skewed by the inclusion of oncology drugs with non-rare indications. PAS has undertaken a similar analysis of the cost of DRDs in Canada. The methods and results are presented below.

4.2 Methodology

The list of 93 drugs identified by the PMPRB was obtained and used as the starting point for the re-analysis. The drugs were first separated by indication type (i.e., oncology or non-oncology). Following this step, the European Medicines Agency's (EMA's) and US Food and Drugs Administration's (FDA's) orphan-designated approvals for all 93 drugs were extracted from public records available through the table of EMA orphan designations[7] (available here) and the FDA Orphan Drug Designation Search[8] (available here). In order to identify oncology drugs with indications that span many small markets which collectively treat a large patient population, these drugs were categorized into two groups: those that had ≤ 2 EMA or FDA orphan-designated approvals and those who had > 2 EMA or FDA orphan-designated approvals. Next, the total number of EMA, FDA, and Health Canada (HC) approved indications were extracted from the latest Summaries of Product Characteristics, product inserts, and product monographs from each regulatory agency, respectively. The approved FDA and EMA orphan-designations were compared and consolidated based on the total number of indications listed in either the HC product monograph, FDA label or EMA

Summary of Product Characteristics (Annex I). Following this, the relevant CADTH recommendations were searched to extract prevalence and incidence estimates for each indication. In cases where the CADTH recommendation did not include prevalence or incidence estimates, a secondary literature search was conducted to estimate the number of Canadians affected by the respective indication(s). Lastly, company newswires were searched for any evidence of positive phase-III clinical trial results, recent EMA and FDA approvals, or indications listed on the FDA or EMA label that have not yet been approved in Canada that are indicative of any new incoming indications.

The typical prevalence rate used to define a disease as orphan is fewer than 50 in 100,000 population. Using this rate, an orphan disease is one that affects ≤ 18,800 people across Canada (assuming a total population of 37.6 million); according to the Canadian Cancer Statistics[9], most cancers meet this definition on an annual basis (***Table 1***). As a result, many suggest defining rare cancers based on incidence instead. According to this definition, a rare cancer is one that has an incidence rate of ≤ 6 per 100,000 (Rare Cancer Europe; National Cancer Institute).[10,11] On that basis, a rare cancer is a one that affects ≤ 2,250 Canadians per year.

Table 1. Canadian Cancer Statistics 2018

Cancer type	Rank	Cases	ASIR
Lung	1	28,600	69.9
Colorectal	2	26,800	66.3
Breast	3	26,500	69.1
Prostate	4	21,300	110.4
Bladder	5	8,900	21.8
Non-Hodgkin lymphoma	6	8,300	20.8
Uterus	7	7,300	35.7
Melanoma	8	7,200	18.5
Thyroid	9	7,100	19.0
Kidney and renal	10	6,600	16.5
Leukemia	11	6,200	15.5
Pancreas	12	5,500	13.5
Oral	13	4,700	11.9
Stomach	14	3,500	8.6
Brain/CNS	15	3,000	7.8
Multiple myeloma	16	2,900	7.1
Ovary	17	2,800	13.7
Liver	18	2,500	6.1
Esophagus	19	2,300	5.7
Cervix	20	1,550	8.3
Larynx	21	1,150	2.8

Testis	22	1,100	6.1
Hodgkins lymphoma	23	990	2.7
All others	24	19,500	48.5

Canadian Cancer Statistics 2018. Available here

For this analysis, oncology drugs that target a total estimated patient population that exceeds 2,250 incidence cases per year and/or drugs that have a large pipeline of incoming indications were classified as non-orphan.

4.3 Results

Number of Oncology versus Non-Oncology Orphan Designated Drugs

From the PMPRB list of 93 EDRDs, 48 were classified as oncology drugs and 43 as non-oncology. Two oncology treatments were excluded as they were combination therapies that included drugs that were also included as monotherapies (Opdivo + Yervoy; Mekinist + Tafinlar). Of the 48 oncology drugs remaining, 34 had ≤2 EMA/FDA approved orphan drug indications, while the remaining 14 had >2 EMA/FDA approved orphan drug indications.

lists the non-oncology drugs identified in the PMPRB list of 93 EDRDs. ***Table 2*** lists the oncology drugs identified in the PMPRB list of 93 EDRDs, which are further classified as oncology drugs that have ≤ 2 or > 2 EMA/FDA approved orphan-designated indications.

Table 1. Non-oncology drugs (43/93) included in the PMPRB analysis

Aldurazyme	Firazyr	Naglazyme	Replagal
Brineura	Galafold	Nplate	Soliris
Carbaglu	Revestive	Onpattro	Spinraza
Cerdelga	Hemlibra	Orfadin	Strensiq
Cerezyme	Idelvion	Orkambi	Symdeko
Cinryze	Ilaris	Pheburane	Takhzyro
Crysvita	Juxtapid	Procysbi	Tegsedi
Defitelio	Kalydeco	Prolastin-C	Vimizim
Elaprase	Kanuma	Radicava	Vpriv
Elelyso	Kuvan	Ravicti	Zavesca
Fabrazyme	Myozyme	Remodulin	

Table 2. Oncology drugs (48/93) included in the PMPRB analysis

Drugs with ≤2 EMA/FDA approved orphan drug designation (34/48)			
Alecensaro	Folotyn	Ninlaro	Yondelis
Alunbrig	Iclusig	Oncaspar	Zelboraf
Atriance	Idhifa	Rydapt	Zolinza

Bavencio	Istodax	Tagrisso	Zykadia
Besponsa	Kymriah	Trisenox	
Blincyto	Kyprolis	Unituxin	
Calquence	Lartruvo	Vitrakvi	
Clolar	Lorbrena	Xalkori	
Cotellic	Luthathera	Xospata	
Empliciti	Mekinist	Yescarta	
Drugs with >2 EMA/FDA approved orphan drug designation (14/48)			
Adcetris	Imbruvica	Opdivo	Yervoy
Avastin	Keytruda	Pomalyst	Zejula
Cyramza	Lynparza	Revlimid	
Darzalex	Mylotarg	Venclexta	

Total Target Patient Population Per Year Among Orphan Designated Oncology Drugs

Of the 14 oncology drugs with > 2 approved orphan indications, more than half (8) have a collective target population that exceeds 2,250 cases per year and would not likely be considered rare under a Canadian definition. Also, one of the 34 oncology drugs with ≤ 2 approved orphan indications had a collective target population that exceeded this threshold.

Furthermore, from the total of 48 oncology drugs, 24 had at least one expected new indication or expanded indication which was informed by either recent positive phase-III clinical trial outcomes, recent FDA or EMA approvals, or indications listed on the FDA or EMA label that have not yet been approved in Canada. ***Table 3*** outlines the total number FDA/EMA orphan-designated and approved indications, the total number of FDA/EMA/HC approved indications and the estimated incidence cases in Canada.

In total, at least nine of the oncology drugs should not be considered DRDs because they exceed the threshold of 2,250 cases per year. Additionally, half (24 of 48) of the oncology drugs could expect additional indications not yet registered in Canada to be approved in the near future. The nine drugs that have an incidence rate that exceeds the definition of rare are highlighted in yellow. All nine could be expected to have additional approved indications in a relatively short term. In addition, a further 13 could be classified as rare now but are anticipating additional indications to be approved soon; those 13 drugs are highlighted in orange.

Table 3. Number of approved EMA/FDA orphan indications, total number of EMA/FDA/HC indications and estimated incidence cases per year

Drugs	EMA *orphan/total*	FDA *orphan/total*	HC *total*	Potential number of incoming indications	Incidence *cases/year (link to stats)*	References
Drugs with > 2 EMA/FDA approved orphan drug designation (14/48)						
Adcetris	3/6	7/6	6	0	1000 (HL) 560 (PTCL-Nos, sALCL, AITL) 425 (CTCL)	EMA; FDA; HC
Avastin	0/10	7/7	5	1	4880 (CRC) 2500 (NSNSCLC) 2200 - 2800 (ovarian cancer; epithelial) 1500 (GB)	EMA; FDA; HC
Cyramza	0/6	2/5	1	4	1500 (metastatic esophago-gastric adenocarcinoma)	EMA; FDA; HC
Darzalex	4/4	6/6	3	2	<2900 (MM)	EMA; FDA; HC
Imbruvica	3/4	6/6	9	1	2400 (CLL) 400 to 500 (MCL) 832 (NHL; remission; MZL) 113 to 188 (WM) N/A (cGVHD)	EMA; FDA; HC
Lynparza	0/3	5/7	5	2	<1920 (stage II/IV ovarian cancer) <2380 (relapse ovarian cancer) <167 (BC; metastatic)	EMA; FDA; HC
Mylotarg	0/1	2/2	1	1	1675 (AML)	EMA; FDA; HC
Opdivo	0/9	7/11	11	1	<6800 (meta melanoma) 7200 (adj melanoma) <16717 (CAN Cancer) 1500 (RCC) <3762 (head & neck) <1000 (CAN Cancer: HL)	EMA; FDA; HC

Drugs	EMA *orphan/total*	FDA *orphan/total*	HC *total*	Potential number of incoming indications	Incidence *cases/year (link to stats)*	References
					<1400 (HCC; ASCO)	
Pomalyst (US/CAN)/Imnovid (EU)	1/2	2/2	2	1	<2900 (MM)	EMA; FDA; HC
Revlimid	0/6	5/5	2	4	1316 to 1842 (Myelodysplastic Syndromes) <2900 (MM)	EMA; FDA; HC
Venclexta (US/CAN)/Venclyxto (EU)	0/3	2/2	3	0	2400 (CLL)	EMA; FDA; HC
Yervoy	0/3	2/6	3	3	<6800 (meta Melanoma) ~1052 (RCC)	EMA; FDA; HC
Zejula	1/1	3/3	1	2	<1860 (ovarian)	EMA; FDA; HC
Drugs with ≤ 2 EMA/FDA approved orphan drug designation (34/48)						
Alecensaro (CAN)/Alecensa (EU/US)	0/2	1/1	2	0	460 (ALK+ NSCLC)	EMA; FDA w/ c; FDA; HC
Alunbrig	0/2	1/1	1	1	460 (ALK+ NSCLC)	EMA; FDA w/ c; FDA; HC
Atriance (EU/CAN)/Arranon (US)	0/1	1/1	1	0	<385 (ALL)	EMA; FDA; HC
Bavencio	0/2	1/3	1	1	300 (mMCC) 2000* (UC)	EMA; FDA; HC
Besponsa	1/1	0/1	1	0	<385 (ALL)	EMA; FDA; HC
Blincyto	1/3	2/2	3	0	<385 (ALL)	EMA; FDA; HC
Calquence	1/0	1/2	3	1	<2400 (CLL) 400-500 (MCL)	EMA; FDA; HC
Clolar (CAN/US)/Evoltra (EU)	0/1	1/1	1	0	<385 (ALL)	EMA; FDA; HC

Drugs	EMA *orphan/total*	FDA *orphan/total*	HC *total*	Potential number of incoming indications	Incidence *cases/year (link to stats)*	References
Cotellic	0/1	1/1	1	1	320 (Melanoma; metastatic)	EMA; FDA; HC
Empliciti	0/2	2/2	1	1	<2900 (MM)	EMA; FDA; HC
Folotyn	1/0	1/1	1	0	600 (PTCL)	EMA; FDA; HC
Iclusig	2/2	2/2	2	0	<385 (ALL) 600 (CML)	EMA; FDA; HC
Idhifa	0/0	1/1	1	1	1675 (AML)	EMA withdraw; FDA; HC
Istodax	1/0	2/2	1	0	600 (PTCL)	EMA refusal; FDA; HC
Kymriah	2/2	2/2	2	0	<385 (ALL) <2000 (DBCL)	EMA; FDA; HC
Kyprolis	1/1	1/2	1	1	<2900 (MM)	EMA; FDA; HC
Lartruvo	0/0	1/1	1	0	<1025 (STS)	EMA; FDA; HC
Lorbrena (CAD/US)/Lorviqua (EU)	0/1	1/1	1	0	460 (ALK+ NSCLC)	EMA; FDA; HC
Lutathera	1/1	0/1	1	1	<2203 (GEP-NET)	EMA; FDA; HC
Mekinist	0/4	2/4	1	1	320 (Melanoma; metastatic)	EMA; FDA; HC
Ninlaro	1/1	1/1	1	4	<2900 (MM)	EMA; FDA; HC
Oncaspar	0/1	1/2	1	0	<385 (ALL)	EMA; FDA; HC
Rydapt	2/2	2/2	2	0	1675 (AML) 460 (mastocytosis; mast cell leuk)	EMA; FDA; HC

Drugs	EMA *orphan/total*	FDA *orphan/total*	HC *total*	Potential number of incoming indications	Incidence *cases/year (link to stats)*	References
Tagrisso	0/2	1/2	2	0	3283 (EGFR+ NSCLC)	EMA; FDA; HC
Trisenox	0/2	2/2	1	0	168 (AML; APL)	EMA; FDA; HC
Unituxin	0/0	1/1	1	0	40 (Neuroblast)	EMA withdraw; FDA; HC
Vitrakvi	0/1	1/1	1	1	1856 (total cancer; blood cancer; NTRK)	EMA; FDA; HC
Xalkori	0/3	2/2	2	0	460 (ALK+ NSCLC) 195 (ROS NSCLC; advanced)	EMA; FDA; HC
Xospata	1/1	1/1	1	0	1675 (AML)	EMA; FDA; HC
Yescarta	2/2	4/4	4	1	<2000 (DBCL)	EMA; FDA; HC
Yondelis	0/2	1/1	2	0	<2380 (platinum sensitive ovarian) 200 (liposarcoma/ leiomyosarcoma)	EMA; FDA; HC
Zelboraf	0/1	2/2	1	1	320 (Melanoma; metastatic)	EMA; FDA; HC
Zolinza/Vorinostat (EU)	0/0	1/1	1	0	416 (NHL; CTCL)	EMA withdraw; FDA; HC
Zykadia	0/2	2/2	2	0	460 (ALK+ NSCLC)	EMA; FDA; HC

4.4 Discussion and Conclusions

As noted in the results section, at least nine oncology drugs should not be considered rare and almost half the total number of rare oncology drugs (24 of 48) could expect additional indications to be approved in the near future, although they are not yet registered in Canada. Thus, overall, a significant portion of oncology drugs may not be rare and should not be included in an examination of the "escalating" costs of DRDs.

It should be noted as well that the FDA has granted a significantly larger number of orphan designations than the EMA. Of the 48 oncology drugs, all were granted an FDA orphan-designation, while only 18 received an EMA orphan-designation. This supports the findings of a recent paper[12] (available here) which concluded that the FDA grants orphan designations more liberally compared with the EMA. This is due to the European Union requiring new drugs targeting rare diseases to earn an orphan designation by demonstrating a significant benefit compared to competing drugs. For this reason, the FDA list of orphan drugs may not be the most reliable source of orphan-designated drugs according to a Canadian definition of orphan.

Overall, any study evaluating the cost of DRDs in Canada should focus on the DRDs only. This does not preclude a separate analysis of rare and non-rare oncology drug pricing and expenditures.

5. PUTTING COSTS OF DRDS IN CANADA INTO PERSPECTIVE WITH THE FUNDING OF OTHER PUBLIC AND PRIVATE EXPENDITURES

5.1 Introduction

Patient Access Solutions (PAS) undertook an analysis of the current and future budget impact of DRDs in Canada[13]; presented at the 2019 International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Meeting in Copenhagen (available here). The purpose of the analysis was to quantify the expected cost of DRDs in Canada for the most recent year of data available and for the future.

5.2 Methods

For the PAS analysis of the current DRD expenditure, claims data were obtained from PDCI Market Access. The cost of non-oncology DRDs was included, while cancer drugs were excluded for the same reasons as outlined in the analysis above. Namely: non-oncology DRDs are used lifelong while oncology drugs are used for a more limited duration of treatment; CADTH has recognized the differences between oncology and non-oncology drugs and reviews them through different pathways. Cancer drugs usually are approved for more than one indication and/or more than one line of therapy superseding the initial "orphan" designation. The prevalence of cancers typically increases over time, while rare diseases are genetic aberrations and rates of inheritance are more stable.

The analysis addressed public drug program expenditure only.

The cost of drugs not available in the claims database were obtained through Freedom of Information requests in order to ensure the most complete data collection possible. The cost of non-EDRDs (i.e., drugs with annual treatment costs <$100k) were included as well.

5.3 Results

A high-level view of the results is shown in this section. The full analysis is included as an appendix.

Figure 1 shows the increase in DRD expenditure by public payers in Canada over time. By 2019, the total annual expenditure was $280 million.

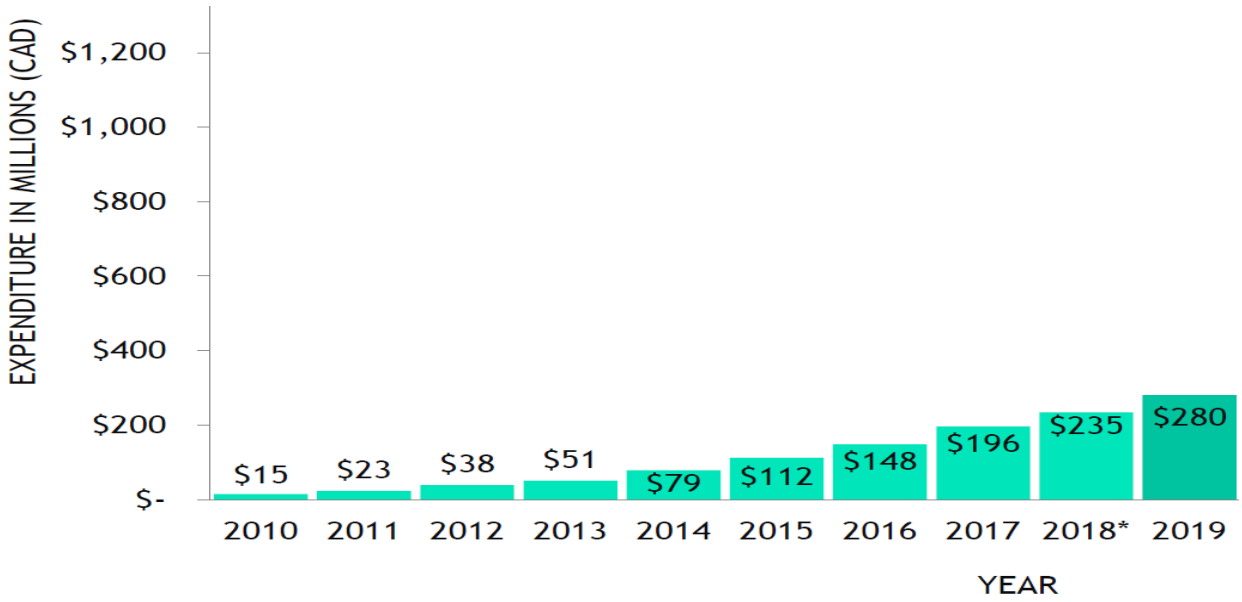

Figure 1. Total annual DRD expenditure in Canada by public payers

Figure 2 shows that the current expenditure on DRDs in 2019 was equivalent to about 2% of the total pharmaceutical expenditure in Canada. This figure is similar to the amount (2.5%) reported by the PMPRB for 2019 for private and public payers combined.

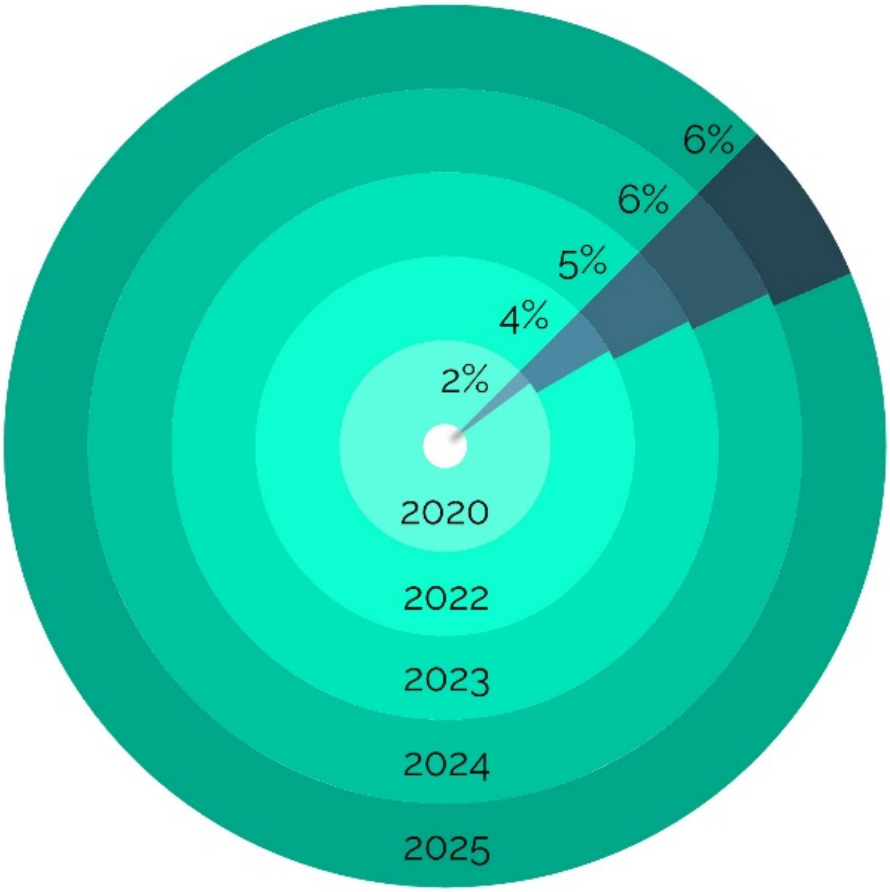

Figure 2. Total annual DRD expenditure in Canada as a percentage of total pharmaceutical spend

Figure 3 puts the annual expenditure on DRDs ($280M) into important context when compared with the cost of drugs for smoking related illness ($1B) and the total cost of other public health spending ($175B). This analysis also demonstrates the choices of Canadians with regard to non-essential medical spending on cosmetic procedures ($1.5B) and recreational cannabis ($1.6B). These results indicate that the annual public cost of DRDs is exceedingly small when compared with other benchmarks of public government and private/societal non-essential health spending.

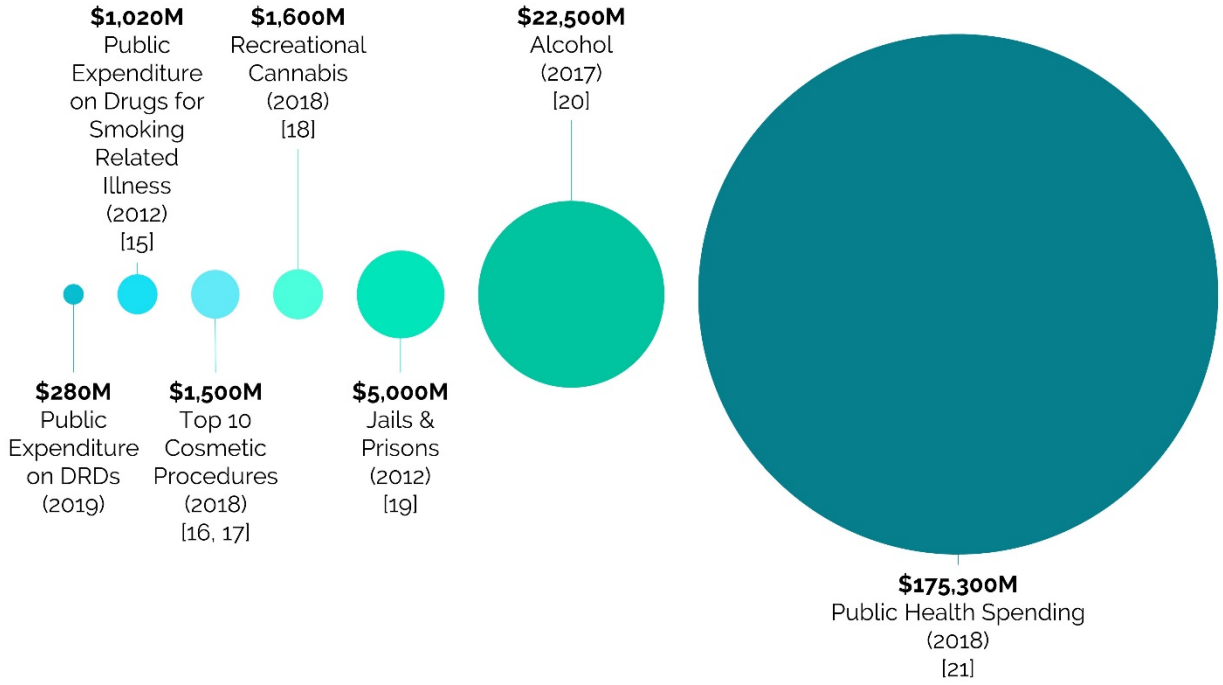

Figure 3. Comparison of the annual cost of DRDs in Canada with annual expenditures in other public and private health spend

Any determination of pricing that could affect the availability of new DRDs in Canada should be based on a fully informed public consultation that offers important context.

6. HIGH LEVEL CRITIQUE OF THE PROPOSED PMPRB GUIDELINES

Numerous aspects of the current version of the draft PMPRB guidelines must be altered in order to ensure that Canadians will continue to have access to these important medications. The two most important limitations of the proposed guidelines in relation to the manner in which they risk the entry of new DRDs in Canada is described below.

6.1 The Pharmacoeconomic Value Assessment will Limit the Number of Drugs that will be Launched in Canada

High cost drugs are the only ones subject to a pharmacoeconomic value test, with DRDs being the most likely to fall into that category. The pharmacoeconomic value test disadvantages DRDs, especially those that target ultra-rare diseases. As noted in Section 3.5, ICERs used to evaluate DRDs almost always far exceed the $150k and $200k thresholds proposed by PMPRB. In addition, no concessions are made for differences in prevalence between rare, ultra-rare, and moderately rare indications. Using the typical definition of rare in Canada (i.e., 50 per 100,000 population), a rare disease is one which affects fewer than about 18,800 individuals (assuming a total population of 37.6 million). Some DRDs are known to target only 10 patients in Canada. It will be highly unattractive for manufacturers to bring drugs to rare disease markets that are extremely small with target ICERs $\leq$ $200,000. The point at which market entry in Canada will become infeasible is not known. While individuals with rare conditions are already disadvantaged relative to the average citizen, this proposed ICER threshold will further disadvantage individuals with very rare conditions (i.e., $\leq$ 2 per 100,000).

In addition to not distinguishing between differing levels of rarity, relying on the CADTH re-analysis of ICERs is problematic in that the majority of re-analyses result in ICERs that are 2- to 4-fold higher than those submitted to CADTH by manufacturers. At the very least, an arms-length panel of clinical and economic experts should be relied upon to determine the most reasonable assumptions/inputs into the economic model before CADTH makes its recommendations. These results should be made public before the PMPRB utilizes them for price-setting purposes.

6.2 The Therapeutic Value Assessment will Limit the Number of Drugs that will be Brought to Market in Canada

The therapeutic value assessment also unfairly disadvantages DRDs because most will be classified as Level 1 or Level 2 products under the PMPRB's new therapeutic classification system. By PMPRB's own analysis, the majority of DRDs are deemed to offer moderate to little or no additional value compared with current treatment alternatives. This means that the required price reductions for most DRDs will be in the order of 40%-50% lower than the new maximum list prices.

Again, there is no distinction between rare and ultra-rare drugs and it is expected that the certainty of clinical value decreases as the rarity of the target patient population increases. This is effect can be attributed to smaller trial sizes, lack of an appropriate comparator arm, and lack of validated efficacy and quality of life measurement tools.

To date, there has been no suggestion that the determination of therapeutic value will be a transparent process involving multiple stakeholders (i.e., patients, caregivers and clinicians) in the review. Without including the patient voice in the assessment of therapeutic value, erroneous conclusions will be made and DRDs will not be available for those in need.

6.3 Context Regarding the Impact of the Bias Against DRDs in the Current Proposed Guidelines

Highly unpredictable net pricing due to pharmacoeconomic and therapeutic value uncertainty makes market entry highly unattractive for DRDs in Canada. While RAREi understands that the

rationale behind ensuring that a large budget is not spent on a small number of individuals, the proposed guidelines virtually ensure that individuals who require the rarest drugs will not be able to access them.

With strict pharmacoeconomic and therapeutic value targets, the unique mechanisms of providing value to payers that, in turn, provides additional value to patients will be lost. Manufacturers of DRDs currently invest in patient support programs, early access programs, and registries to ensure that patients are supported and are able to access drugs immediately after Health Canada approval. These investments also allow manufacturers to continue to measure outcomes which helps ensure that these drugs are providing value in the very long term. If highly restrictive price limits are enforced in the future, these supportive programs may be scaled back in search of a solution that reduces expenditures for the manufacturer.

In summary, in the search for "equity" across all Canadians, the individuals born with genetic conditions through no fault of their own will be treated less equally than individuals that chose to smoke or overeat or avoid exercise simply because the drugs that treat those conditions are not rare. This logic is non-sensical and the analyses that support this backward thinking must be discarded.

7. CONCLUSION

PMPRB guidelines, in their current form, are not set up to ensure equity for Canadians most in need of novel treatments. PMPRB was founded on a principal of achieving median prices in Canada; the proposed guidelines appear aimed at achieving prices far below the median. As shown in the PMPRB's own research report, the cost of Canadian DRDs is already closer to the median of the OECD countries and that is without considering the confidential rebates. Further decreases in DRD prices will mean that Canadians will not have access to the important treatments that are available in other OECD nations.

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