RAREi
THE CANADIAN FORUM FOR RARE DISEASE INNOVATORS

Submission to House of Commons Standing Committee on Health (HESA)

Restoring Hope to the Canadian Rare Disease Community

HESA's review of Canada's pharmaceutical price controls

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About RAREi

RAREi is an informal network of research-based bio pharmaceutical innovators committed to monitoring, responding and shaping policy issues in the Canadian rare disease environment. The members of RAREi are Alexion Pharma Canada Corp., Amicus Therapeutics, Inc., Biogen Canada Inc., Biomarin Pharmaceutical Inc., Horizon Therapeutics Canada, Ipsen Biopharmaceuticals Canada Inc., Mitsubishi Tanabe Pharma Canada Inc., Recordati Rare Diseases Canada Inc., Sanofi Genzyme, Sobi Canada Inc., Ultragenyx Pharmaceutical and Vertex Pharmaceuticals (Canada) Inc. For more information, see www.rarei.ca.

1. Introduction

On behalf of the Canadian Forum for Rare Disease Innovators (RAREi), we congratulate the committee for undertaking this important study examining the federal government's pharmaceutical price regulatory reforms. This study is the first opportunity for parliamentary scrutiny of the reforms which fundamentally alter the role of the Patented Medicine Prices Review Board (PMPRB).

The main changes will allow the PMPRB to implement aggressive new price controls for patented medicines, through: 1) changes to the basket of countries used to compare medicine prices

internationally[1] and 2) the addition of several new economic factors, including pharmacoeconomic value and the size of market which would be used as tools to control prices.

RAREi members have been concerned with the changes underway since they were first proposed several years ago. And despite consistent ongoing efforts to address those concerns that have been raised in the context of consultations and external research by hundreds of affected stakeholders, we remain as worried about the implications today as we were when they were initially announced. To be more precise, RAREi has followed and participated in the PMPRB consultation process whenever offered the opportunity to contribute. In doing so, it has raised many specific concerns with respect to rare disease and patient access to treatment. Despite these efforts, we do not feel that our concerns and suggestions have been given appropriate consideration by the PMPRB. And we are not alone in that assessment. Most of the concerns and suggestions raised by stakeholders have gone unanswered by the board.

In this context, RAREi is encouraged that the committee has decided to review these reforms. We hope your deliberations will lead to a report that conveys stakeholder concerns and provides clear and implementable recommendations to the government.

In sum, RAREi members believe the new federal pricing regime will create substantial market uncertainty, effectively delay or eliminate patient access to important new vaccines and therapeutics, undermine Canada's life sciences ecosystem and impose unreasonable new bureaucratic barriers to entry for all medication developers. The changes are particularly challenging for rare disease treatment innovators.

Ultimately, we are calling on the federal government to revisit its new price control regime and work with affected stakeholders to arrive at a long-term, certain and sustainable approach for pharmaceutical price regulation in Canada in a way that will achieve the government's objectives without undermining a vital and vibrant industry sector that is committed to meeting the needs of rare disease patients in Canada.

As an immediate first step, RAREi recommends that the federal government remove the new economic factors from the *Patented Medicines Regulations* in recognition of their significant negative impact on access to rare disease treatments and clinical trials, for reasons that are set out below.

As RAREi previously expressed in a submission to this committee during its February 2019 *Barriers to Access to Treatment and Drugs for Canadians Affected by Rare Diseases and Disorders* study, Canadians already experience exceptional challenges in trying to obtain access to treatments for rare conditions.

The August 2019 revisions to the *Patented Medicines Regulations*, and the October 23, 2020 release of associated new PMPRB guidelines, which will be used to implement those regulatory measures, will exacerbate these existing problems, and severely undermine federal and provincial government efforts to improve access to medicines for Canadians with rare diseases.

That's because the amended regulations give the PMPRB the power to implement aggressive price controls without any opportunity for negotiation, based on the application of new economic factors, that will lead to steep price reductions for almost all patented medicines. It is expected that public list prices for all patented medicines will fall initially by substantial amounts (recent projections range from 15-30%

[1] The previous basket included the US, Switzerland, Sweden, the UK, France, Germany and Italy. The new basket removes the US and Switzerland and adds Belgium, the Netherlands, Spain, Norway, Japan and Australia.

off the current list prices) on average, while medications deemed high-cost or high-volume could be subject to additional price cuts of 50% or more from already reduced public list prices.

Such drastic price reductions will simply deter many innovators from bringing new medicines to Canada and will be particularly damaging to rare disease innovators, many of which are small and medium-sized Canadian biotechnology companies. For medicines that serve small patient populations, it will be harder to: 1) absorb such price reductions in the context of requirements to invest in medical, sales, regulatory and other key steps required to deploy new medicines; 2) provide treatments on compassionate grounds; and 3) comply with the new burdensome rules.

2. Summary of RAREi's concerns with the PMPRB guidelines

RAREi's views about the PMPRB's proposed approach to implementing the new regulations may be summarized as follows:

a. Lack of special consideration for rare disease treatments

RAREi is disappointed that the guidelines do not contain any accommodation to recognize the unique characteristics of rare disease treatments or provide any incentive for their commercialization and development in Canada.

Instead, all patented medicines will be subject to the same severe price reductions and similar administrative and cost burdens necessary for complying with the PMPRB's complicated new price review regime (which became more complex and uncertain with each new version of the guidelines).

We believe that the new reporting requirements would be particularly onerous for the small and medium-sized companies primarily dedicated to addressing the needs of rare disease patients that make up most of RAREi's membership.

Frankly, it is surprising that that no effort was made in the guidelines to acknowledge and account for the additional challenges represented by rare diseases in light of the increasing willingness of different Canadian governments to find ways to facilitate the reimbursement of, and improve access to, rare disease therapies.

The federal government has previously committed to spearheading and funding a national rare disease strategy, recognizing that "special consideration" is required to ensure a nationally consistent approach for these medications. It repeated that pledge as recently as September 23, 2020 in its throne speech.

In addition, there are ongoing active efforts at the provincial-territorial level to find new approaches to improving publicly funded access to rare disease medicines via the Expensive Drugs for Rare Diseases Working Group. And Quebec has made improving access to rare diseases a provincial priority, announcing that it plans to pilot test the application of a customized evaluation framework for rare disease treatments in the next few years.[2] Quebec's health technology assessment (HTA) agency, INESSS has also

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

recently broadened the lens through which it assesses the value of rare disease medicines by introducing the notion of "promising value" as part of its product reviews.[3]

All things considered, the lack of distinct consideration for rare disease treatments seems inconsistent with the prevailing winds driving rare disease policy in Canada of late.

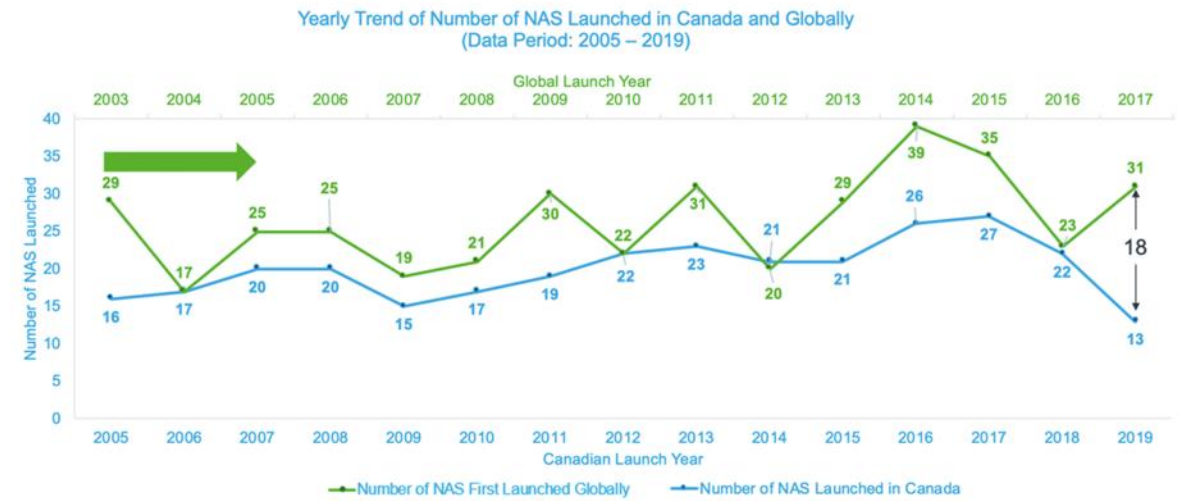
b. Impact of severe mandated price reductions

Price reductions for patented rare disease medicines under the new regime would be in the 45-75% range, which are levels that are much higher than what Health Canada forecasted when it first outlined its new price review approach.

Such significant price cuts would lead to Canada being deemed a late-tier launch country globally. That is also making it significantly more challenging for Canadian affiliates to undertake research here, including clinical trials.

The consequences of the proposed changes are already being felt. Even before the regulatory changes are in effect, the uncertainty created by these amendments is having an impact on access to new medicines. For example, in 2019, there was a significant decline in the number of new medicines coming to market. The 22 products launched in 2018 declined to only 13 in 2019, despite an overall increase in the number of launches globally during the year (see Figure 1).

Figure 1



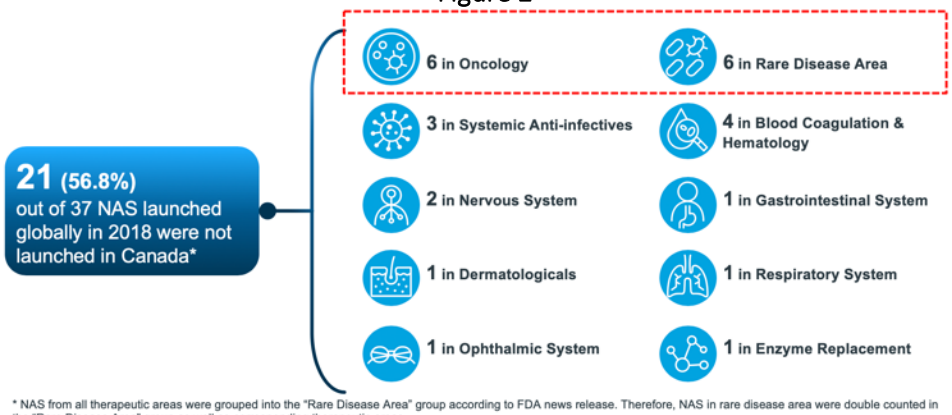
IQVIA MIDAS Database, all new launches within Jan 1, 2000 – Dec 31, 2019 (Data extracted on Mar 13, 2020). Top 25 countries based on 2019 sales. Austria and Sweden were excluded due to launch data quality. NAS: New active substance

Source, IQVIA, New Medicine Launches: Canada in a Global Context, June 2020: https://lifesciencesontario.ca/wp-content/uploads/2020/06/EN_LSO_Global-Launch-Benchmarking_Webinar-June22-20_Final.pdf

To clarify, of the 21 medicines that were launched globally, but not in Canada in 2018, most were used to treat cancer and rare diseases (see Figure 2).

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

Figure 2

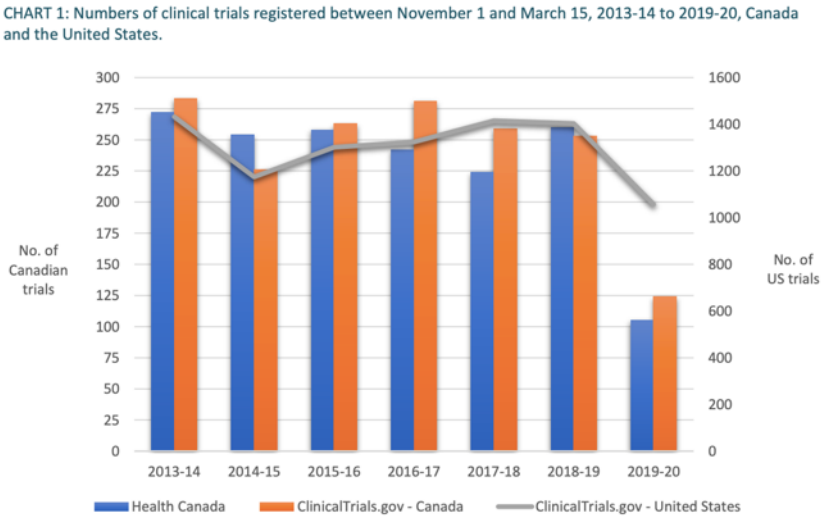


* NAS from all therapeutic areas were grouped into the "Rare Disease Area" group according to FDA news release. Therefore, NAS in rare disease area were double counted in the "Rare Disease Area" group as well as corresponding therapeutic areas.
1 NAS was grouped into "Others" and not listed here.
IQVIA 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

Source, IQVIA, New Medicine Launches: Canada in a Global Context, June 2020: https://lifesciencesontario.ca/wp-content/uploads/2020/06/EN_LSO_Global-Launch-Benchmarking_Webinar-June22-20_Final.pdf

In addition, the number of trials registered by Health Canada from November 2019 to mid-March 2020 fell by 52% compared to the average number registered during the same period in the previous six years. The number of new clinical trials also fell in the US during the same time frame, but only by 21% (see Figure 3).

Figure 3



In addition, to their direct impact on patentees, those changes also would have negative implications for numerous research institutes, academic health centre research arms, contract manufacturing and research operations and early-stage pharmaceutical developers that all rely on the innovative pharmaceutical industry for much of their prosperity.

c. Inappropriate use of economic factors to set market prices

From RAREi's perspective, the most problematic aspect of the pending regulatory changes are the new economic factors included in the August 2019 amendments (i.e., pharmacoeconomic value, market size,

and GDP/GDP per capita). The mandatory economic factors create a complex, punitive and unpredictable pricing framework that will block reasonable pathways to commercialization of new treatments, thereby depriving Canadian patients of access to important new medicines.

In terms of the new pharmacoeconomic factor, RAREi has 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 regulate maximum prices for an entire jurisdiction. For this reason alone, they should be abandoned by Health Canada as a means of determining an acceptable price.

Moreover, rather than relying on ICURs submitted by the innovator, the PMPRB intends to use reinterpretations of ICURs submitted by innovators to the Canadian Agency for Drugs and Technologies in Health (CADTH) as the basis of its price-setting. CADTH's re-analyses often result in ICURs that are substantially 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.

As it is, the current HTA review process fails to account for the unique characteristics of rare disease treatments, including the small size of clinical trials and the fact that long term randomized control trials are often not possible for life-threatening conditions. In addition, CADTH reviews are not flexible enough to accommodate informed therapeutic and/or current patient management knowledge in a specific therapeutic area or for a given condition. Therefore, in the context of rare disease medicines particularly, standard pharmacoeconomic methods used in HTA are not well-suited for evaluating these treatments. The result is greater uncertainty compared to treatments for more common illnesses and higher ICURs.

Many experts have recognized the limitations of using ICURs generally, and especially in the context of rare disease treatments. According to a study that reviewed the impact of ICURs on the assessment of ultra rare disease (URD) medicines, "many interventions for rare and URDs are unlikely (or altogether unable) to meet standard … benchmarks." It concluded that there is a strong need for alternative economic evaluation models for URDs.[4] No other country has implemented a health economic approach to regulating prices of medications. Yet, Health Canada insists on using this controversial and uncertain mechanism to set maximum prices for rare disease medicines.

RAREi also objects to the use of market size to further ratchet down the prices of medicines. This factor is completely irrelevant to and disconnected from the PMPRB's mandate to determine price excessiveness and should not be used in tests to set pricing ceilings.

This inappropriate and punitive regulatory measure will fundamentally discourage innovation, effectively regulating revenues as opposed to price. While the market size adjustment thresholds were changed

[4] Schandler M et al, *Incremental cost per quality-adjusted life year gained? The need for alternative methods to evaluate medical interventions for ultra-rare disorders.* Journal of Comparative Effectiveness Research: Res. (2014) 3(4), 399–422: https://www.ncbi.nlm.nih.gov/pubmed/25275236. See also National Council on Disability, *Quality-Adjusted Life Years and the Devaluation of Life with Disability,* November 6, 2019: https://ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf.

during the guidelines consultations, the ultimate price ceiling lowering mechanism remains unreasonably punitive and at the broad discretion of PMPRB staff and the board.

d. Price uncertainty

While the issues mentioned above represent significant barriers to new innovations, perhaps the most challenging aspect of the new regime for Canadian affiliates will be the pricing uncertainty that follows.

Imagine a scenario where a Canadian general manager of a rare disease innovator company is trying to establish an acceptable launch price for approval by his/her global leadership.

Under the new PMPRB rules, the starting point is a price that must be equal to or less than the *median* price among a new basket of comparator countries that excludes selected jurisdictions that are deemed too high-priced. That will immediately result in a substantially lower price (likely between 15-30%) than previously had been acceptable.

Subsequently, if the product is expected to sell more than $12 million in annual sales and costs more than about $90,000 per year, the price would be subject to additional reductions of between 20-50% off the new lower base. Except that the precise amount of the additional discount can't be determined right away. The determination of how much more must wait until after CADTH completes its HTA review and issues a final reimbursement recommendation, a process that typically takes at least six months post-launch.

In addition, if the product can be expected to achieve more than $50 million in sales, the allowable selling prices would be reduced further by an additional 25% from the already reduced price. And when it reaches more than $100 million in sales, a subsequent 35% reduction would be required, driven by the uncertain pharmacoeconomic factor as explained in the section above.

Even if the product is not deemed a high-cost medicine, but still manages to achieve the $50 and $100 million sales benchmarks, additional reductions off the list price would be required as outlined above.

And if all that were not enough, the PMPRB's new reassessment framework allows for the selling price to be reconsidered as market dynamics change, meaning that the allowable price could change numerous times within a short span of time.

The end result is an incalculable allowable price and real challenges for the innovator in establishing an acceptable launch price that would provide the kind of pragmatic information required to comply with global market projection calculations for the medicine internally.

The inability for a Canadian 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. This will make it very challenging for innovative companies to bring rare disease medicines to the Canadian market, which means the reforms would end up further slowing down or limiting patient access to new rare disease treatments.

Despite RAREi having clearly identified a number of problematic issues with the guidelines and the overall approach to regulating rather than establishing reasonable price ceilings in its submissions to the PMPRB, the most concerning aspects remain unresolved.

While we acknowledge that some minor alterations were made during the consultation process, the core of the pricing regime remains virtually identical to what was originally proposed by the board. The proposed changes in the October 23 final guidelines are also subject to change based on the outcomes of an anticipated judicial review appeal to the Federal Court of Appeal. This means they are both limited and provisional.

3. Additional concerns

a. Lack of independence and neutrality

The PMPRB's communications during the consultation phase have not met the expected standards of a regulator to be objective, impartial, consistent and without conflict of interest or bias. In particular, it has been combative with stakeholders and dismissive of numerous concerns expressed throughout the process. It also used its research unit to advocate for the board's perspectives on the proposed new price review regime by undertaking analyses that appear expressly designed to rebut common stakeholder criticisms of its approach. In that latter regard, RAREi commissioned an independent organization to review the PMPRB's research report entitled "*Insight into the spending on expensive drugs for rare diseases."* The analysis, which is contained as an appendix to RAREi's July 2020 submission to the PMPRB,[5] offered an evidence-based response to the PMPRB's findings. It also demonstrated, contrary to the PMPRB's contention that the cost of these medicines is veering out-of-control, that total Canadian spending on non-oncology rare disease treatments 2019 was $280 million, representing just 2% of the national medication spending.[6]

b. Excessive discretion provided to PMPRB officials and the board

As indicated above, RAREi also has issues with the unprecedented level of discretion that the new guidelines confer on board staff. In terms of enforcing the new rules, the guidelines expressly allow staff to revise or ignore the guidelines as they see fit in a given circumstance. Paragraph 8 of the PMPRB guidelines state that the board and staff are not bound by the guidelines, and can apply any price test they want when assessing the excessiveness of a given price. This unrestricted discretion will create considerable business uncertainty in that the board will have the right to apply any price test it wants which completely removes any pricing certainty that an innovator might wish to rely on.

In addition, the role of the independent Human Drug Advisory Committee (HDAP) in categorizing the relative inventiveness of new treatment options has been sidelined in favour of staff. 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

[5] Available for download on RAREi's website (www.rarei.ca) and on the PMPRB consultation feedback page: https://www.canada.ca/content/dam/pmprb-cepmb/documents/consultations/draft-guidelines/submission-received/june2020/June%202020%20submission_RAREi_EN.pdf

[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.

responsibility that should be left to independent arms-length clinical experts to determine and for the board staff to follow.

c. Reduced access to patient support, compassionate access and research programs

Finally, RAREi wishes to point out that several unique Canadian mechanisms of providing value to payers, which also provide additional value to patients could be lost when these new rules come into effect. Rare disease innovators currently invest substantially 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 that outcomes will continue to be measured to ensure that the medications are providing value in the very long term. Funding for patient support and compassionate access programs are provided by companies despite the slow, expensive and uncertain process for public drug program evaluation and funding in Canada. Companies take on significant risk in supporting patients with the hope for continuity of therapy and public reimbursement. Among other impacts, forcing down allowable prices as a requirement for entry into the Canadian market will undermine the capacity to negotiate or provide life-saving therapies through patient support programs and compassionate use.

4. Conclusion

At their heart, the proposed federal pharmaceutical price review reforms move the PMPRB away from its traditional role as a monitor against potential price abuse by patentees. Instead the regulations have established punitive 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 typically negotiated between payers and pharmaceutical developers in order to address important value questions. To clarify, RAREi members actively negotiate price concessions and outcomes-based agreements with payers around the world to address affordability and sustainability concerns as a regular way of doing business. These new rules make that process moot.

We acknowledge the alarmist nature of the feedback we have provided to the government, the PMPRB and now to this committee. It reflects the very real and significant long-term effects that we believe will result from these changes. And while it may be easy for the PMPRB to dismiss industry criticism, it must be stressed that the negative feedback communicated about these reforms has been widespread among a range of non-industry voices. Among the more prominent detractors have been patient groups, clinicians, pharmacists, medicine distributors and the life sciences and research communities. Almost 90% of stakeholder submissions provided in the context of the PMPRB's most recent consultation were either opposed to, or raised serious concerns with, the revised guidelines.[7]

Given those concerns, we call on the committee to **recommend that the federal government remove the new economic factors from the *Patented Medicines Regulations***, given that they are the most problematic aspect of the reforms. Most importantly, these factors are not required to generate the savings targeted by Health Canada when the regulatory amendments were originally proposed. In fact, if the federal government were to change only the basket of countries used to compare prices, the list price

[7] PMPRB website, feedback received in response to its revised draft guidelines consultation: https://www.canada.ca/en/patented-medicine-prices-review/services/consultations/draft-guidelines.html

of the vast majority of patented medicines would be reduced by 15% or more, which doesn't even account for current savings achieved through negotiations on listing terms with public and private payers.

This is an extremely exciting time for the rare disease community given the incredible scientific and technological advances in recent years, there is still a lot of work to be done to ensure the benefits of these new technologies reach the Canadian patients who need them. This underscores the importance of the committee's review of these reforms and indicates that it can play a vital role in improving access to needed treatments for the most vulnerable patients in Canada.

We appreciate the opportunity to provide our input and look forward to your report and recommendations on this important health issue. Ultimately, we hope to work with all governments in Canada, patients and clinicians to help ensure that Canadians with rare disorders receive timely access to the health care that they need and deserve. RAREi would welcome the opportunity to participate in any policy dialogue to identify, evaluate and advance a different approach to these reforms.

Appendix – Summary of RAREi's Input on the 2018-19 Rare Disease Treatment Access Study

In its October 2018 submission to the committee, RAREi underscored incredible opportunities for the rare disease community in light of scientific and technological advances emerging. However, we pointed out that there is still a lot of work to be done to ensure the benefits of these new technologies reach the Canadian patients who need them. We detailed the challenges of developing and commercializing rare disease treatments and the limitations represented by the fact that Canada is an outlier among developed countries, without national or even provincial rare disease strategies.

No aspect of the current national medication reimbursement process, including regulatory review and approval, pricing review, HTAs, product negotiations or funding frameworks, is organized to evaluate these treatments appropriately. Moreover, we demonstrated that the current review and approval process is ill-prepared to respond effectively to the new innovative trial designs and adaptive studies that are common when researching new rare disease treatments.

Among other things, RAREi recommended that the federal government implement a new regulatory framework for rare disease treatments that includes incentives to develop and commercialize orphan medicines in Canada and that efforts be made to ensure better and timelier patient access. This included allowing public reimbursement at the time of regulatory approval and increased use of managed access programs and real world evidence that can help address uncertainties related to rare disease medicines. RAREi also asked that the committee encourage the government reconsider its proposed price reforms.

In sum, the PMPRB reforms undermine the work this committee achieved in its 2018-19 study addressing access to rare disease treatments. That review was an important stepping stone to the federal government's Budget 2019 commitment to invest half a billion dollars annually in a national rare disease strategy in Canada starting in 2022-23, a financial commitment echoed in multiple parties' 2019 election platforms, and reiterated in the September throne speech. These initiatives have given the rare disease community hope that access improvements would be forthcoming.

What must be understood clearly is that if the reforms go forward as presently conceived, the promise of a new national strategy or even provincial strategies on rare diseases will be impeded to the point of irrelevance. The national price controls will effectively prevent or at least delay Canadian access to ground-breaking innovative treatments currently in development.