RAREi Responses to Consultation Questions

1. What do you perceive to be the current challenges and barriers facing rare disease medications?

RAREi is a forum for a number of biopharmaceutical companies committed to improving the lives of patients living with rare disorders by researching, developing and commercializing rare disease treatments. The forum includes Alexion Pharma Corp., Biogen Canada Inc., BioMarin Pharmaceutical (Canada) Inc., Horizon Therapeutics Canada, Ipsen Biopharmaceuticals Canada Inc., Shire Pharma Canada ULC, Sobi Canada, Inc., and Vertex Pharmaceuticals (Canada) Inc.

RAREi's purpose is to apply its members Canadian and global experience to inform policy initiatives. We believe that the unique characteristics of rare diseases require a different approach to their evaluation and reimbursement so that Canadian patients can have access to life-saving and life-changing medicines.

RAREi is very pleased that the provincial-territorial (PT) Expensive Drugs for Rare Diseases (EDRD) Working Group recently issued a proposed new approach for facilitating better consideration of complex and specialized medicines – including rare disease treatments – for public reimbursement purposes.

However, while we support the initiative and look forward to collaborating with the working group to develop a robust alternative method for considering public funding of new rare disease treatments, our first recommendation is to change the name of your collaboration to something less focused on price, such as the *Medicines for Rare Diseases Working Group*. The current name, and specifically the term "expensive", unfairly confuses the needs of patients with the list prices of therapies. Canadian health systems have an important opportunity to improve their consideration of the value of investing in these treatments for the benefit of Canada's health system, the knowledge-based economy and, of course, patients and their communities.

Finally, RAREi companies are also members of one or both of BIOTECanada and Innovative Medicines Canada, and provided input into those organization's responses to this survey. This input is intended to complement and supplement the comments of the two industry associations.

Developing treatments for rare disorders is a risky and costly enterprise for several reasons, including poorly understood disease etiology, small patient populations and ethical barriers to conducting randomized controlled trials (RCTs) for life-limiting conditions with no alternative treatments. As a result, rare disease treatments tend to be priced higher on a per-patient basis than medicines for common diseases. In particular, the price difference can be explained in large part by the fact that research and development investments for rare disease treatments have to be recouped from a smaller market worldwide. As well, traditional methods and tools for assessing cost effectiveness are ill-suited for consideration of rare disease treatments and, in fact, systematically set-up a bias against treatments for rare and ultra-rare disorders. This adds

additional challenges to the research and development (R&D) process for rare disease therapies, further increasing the R&D costs.

That said, while rare disease treatments generally result in higher per-patient costs, their overall budget impact is comparatively low given their small patient populations. In particular, based on a 2016 analysis, expenditures for rare disease medicines represented 3.3 to 5.6 % of total Canadian pharmaceutical expenditure in 2007–13, and were expected to remain less than 6 % of total expenditure for the period 2014–18. [1]

In this context, the first barrier we want to raise is regarding the federal government's proposed amendments to the *Patented Medicines Regulations* to change how the federal Patented Medicine Prices Review Board (PMPRB) assesses the prices of patented medicines. If implemented, this proposed reform would have a disproportionate effect on rare disease treatments, and severely reduce the possibility that new innovative therapeutics would be introduced in this country – or at least delay their entry to the Canadian market. As discussed below, it is already very difficult under the current system to commercialize rare disease treatments in Canada. The proposed reform will introduce an additional barrier by establishing a restrictive and uncertain new price assessment process, which could result in price reductions of 70-90% for rare disease medicines.[2] A recently published study clearly shows the negative implications of the reform on rare disease treatments.[3]

There are several other challenges posed by Canada's current regulatory and reimbursement system, which could be greatly improved by including the following specific initiatives:

- a standard definition of a rare disease and designation for orphan drugs
- increased regulatory and/or intellectual property incentives to bring therapies to market
- better alignment between the regulator, health technology assessment evaluators, manufacturers and patients regarding the appropriate criteria against which to measure the performance of a rare disease therapy
- a real world evidence framework and supporting infrastructure to address uncertainties that are inherent in rare disease therapies
- investments to train and develop well-informed clinical expertise in Canada to advise on specific rare diseases and
- increased certainty regarding how to meet the unique needs of rare disease innovations in the context of the current national product listing agreement negotiation process.

That said, RAREi is hopeful that this new proposed supplemental process marks a departure from previous initiatives in which rare disease policy was developed by governments without being implemented, leaving patients and the health system without crucial tools to improve clinical and quality of life outcomes. We look forward to working collaboratively with payers,

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[1] Divino V et al, *The Budget Impact of Drugs Treating Rare Diseases in Canada: a 2007-2013 MIDAS Sales Data Analysis*, Orphanet J Rare Dis,. 2016: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4875716/.

[2] Rawson, N., *Regulatory, Reimbursement, and Pricing barriers to accessing Drugs for Rare Disorders in Canada*", Fraser Institute, 2018: https://www.fraserinstitute.org/sites/default/files/barriers-to-accessing-drugs-for-rare-disorders-in-canada.pdf.

[3] See also Rawson N., *New Patented Medicine Regulations in Canada: Case Study of a Manufacturer's Decision-Making about Regulatory Submission for a Rare Disorder Treatment*, Canadian Health Policy Institute, October 2018 (publication pending at: https://www.canadianhealthpolicy.com/).

regulators, health technology assessment bodies, and patients to develop a system that supports the rare disease community.

Generally speaking, RAREi believes that rare disease treatments should be subject to distinct consideration throughout the Canadian medication regulatory and reimbursement process. Such distinctions should be established in recognition of the unique challenges associated with making rare disease treatments accessible to the patients who need them.

2. From your perspective, does the proposed supplemental process address some or all of the current challenges encountered with complex/specialized drugs, including drugs for rare diseases? Why or why not?

Broadly speaking, the proposed supplemental process potentially could address many key challenges to bringing rare disease therapies to Canadians. However, given that the proposed supplemental process is at an early stage of development, there remain many important details that are essential to understanding the approach that Health Canada, the Canadian Agency of Drugs and Technologies in Health (CADTH), the Patented Medicine Prices Review Board (PMPRB), the pan-Canadian Pharmaceutical Alliance (pCPA) and public drug plans will ultimately take when considering rare disease therapies in Canada.

RAREi is encouraged by the concepts outlined in the proposal and pleasantly surprised by the inclusion of several elements that would improve the current medication review and approval system. These include:

- A system of early determination about whether a given medication would be eligible for consideration within the customized process based on pre-established criteria;
- Concurrent reviews;
- Modifications to the standard health technology assessment process;
- Alterations in the way that national product listing agreement negotiations are approached;
- Enhanced consideration of real-world evidence;
- Individual patient reviews for funding eligibility and
- A commitment by public payers to enhance communications and transparency with all stakeholders throughout the process.

Each of these proposed elements represents important progress. However, the implementation of these concepts is as important as the notion itself. As such, it would be important to engage directly with affected stakeholders in defining the process components carefully and in a manner that enjoys wide support. In this way, it should be possible to develop a flexible and responsive reimbursement system that is properly customized to address the characteristics of these complex treatments and thereby improve health outcomes for rare disease patients in Canada.

The proposed process as currently outlined does not provide enough clarity on the process reforms to be implemented by each of the agencies involved. Those details will ultimately determine whether the proposed process will be seen to address the underlying barriers for patients to access rare disease therapies. For example, while concurrent reviews undertaken by

Health Canada, CADTH and the PMPRB should help reduce timelines – and therefore delays to patient access – if those reviews remain reliant on inadequate screening techniques, evaluation standards and assessment criteria currently in place, patients will continue to experience barriers to access.

Regulatory process

It is unfortunate that the proposed process is not accompanied by a national orphan medication regulatory framework, despite Health Canada's previous efforts to introduce one in 2012.

Health Canada's recently published Orphan Drug Regulatory Approach, which explains innovators' options for seeking regulatory approval and bringing their treatments to patients in Canada, is a positive step forward, but does address the underlying deficits in the current approach and does not reduce the need for a rare disease regulatory framework that includes the key elements adopted by other jurisdictions. These include a definition of "rare disease", an orphan medicine designation process, enhanced market exclusivity, research promotion funds, tax incentives and Health Canada submission fee reductions. These measures would help encourage the development and launch of rare disease treatments in Canada. To clarify, we are not supportive of any reforms that would compromise Health Canada's current high review standards, rather we are seeking modifications that would support and incent the development and introduction of effective rare disease treatments in Canada.

In particular, RAREi endorses the inclusion of a formal definition of "rare disease", such as that used in Europe, which is a disease with a prevalence of 5 in 10,000. A definition and regulatory designation is an important step towards providing clarity to manufacturers at the outset about what will be included in the process and would support alignment with international regulators.

As proposed, the process would rely on certain triggers, such as acceptance of a medication for Health Canada's priority review or Notice of Compliance with conditions pathways, and/or other criteria that are not specified at this time. In light of Health Canada's recently released proposal for an accelerated review pathway, clarity about the additional criteria, such as what is considered to be "significantly high value for patients" or "of high value for public health" is essential to aligning on the supplemental process. As well, it is unclear whether these same criteria will inform prioritization by CADTH and the pCPA.

Also, in order to support better alignment between manufacturers, Health Canada, CADTH, the PMPRB, and the pCPA, there should be a pre-submission consultation session at which all parties to the process could participate in a joint dialogue to assess the available evidence and plan a collaborative approach to meeting everybody's needs as the product goes through the process. Such a session would be best held prior to submission for regulatory review and would support all parties to identify points of uncertainty in the data and the real world evidence (RWE) that could be developed to address those uncertainties. It would also be useful in terms of finding agreement on what manufacturers can provide and the roles of all parties going forward.

Health technology assessment process

In the context of health technology assessment (HTA), early engagement between HTA reviewers and manufacturers to determine how best to assess the medication in light of the available evidence should be a defining feature of the process. This could be addressed at the joint pre-submission consultation proposed above at which uncertainty stemming from the clinical evidence is discussed jointly by the sponsor and evaluators.

In addition, a reimbursement recommendation informed by appropriate criteria for public drug plans should be based on enhanced input from disease-specific clinical experts, practical expectations regarding pharmacoeconomic evidence, and joint development of the associated clinical criteria by HTA reviewers and expert committee members, disease-specific clinical experts (Canadian or international) and manufacturers.

As well, appropriate RWE to support the HTA evaluation should be identified and considered, including available Canadian and international sources of data.

Product listing agreements

RAREi supports the use of innovative frameworks to develop product listing agreements (PLAs) that are appropriate for rare disease treatments. To that end, we call for early engagement between the pCPA and manufacturers to determine jointly what the appropriate target patient population should be, coverage criteria (including start and stop criteria) and reimbursement terms. As with the HTA process above, this could be addressed at a joint pre-submission consultation.

RAREi members have broad experience with different approaches to PLA models used internationally, including portfolio framework agreements, outcomes-based agreements, and other disease-specific agreements. However, in the rare disease space, it is essential that negotiations do not further delay patient access to important therapies. Immediate conditional reimbursement during negotiations would support patient access during negotiations. The development of, and reliance on, RWE should support reimbursement of rare disease therapies without delaying access.

3. What role could you or your organization play in working with others to achieve the stated objective of the proposed supplemental process?

RAREi is broadly supportive of the proposed supplemental process and urges the working group to further customize the process to account for the unique characteristics of rare disease therapies. To this end, the members would be pleased to be a partner in the development of the model. The forum would also welcome the opportunity to host or participate in evaluation and regulatory “sandboxes” designed to test proposed processes with real or hypothetical case studies.

As an effort to demonstrate our support, RAREi proposes the following principles for the development and implementation of such a process.

1) **Put Patients First:** All partners agree that there is a need to help patients with rare disorders access necessary medicines, especially when there is no other treatment option
2) **Start by Talking:** Participants in the process agree to meet early in the process to understand who can be helped and how much it might cost:
    a. How many patients have the disease and may benefit from treatment?
    b. How much would treatment cost on a per patient basis? (vs. list, weight, etc.)
    c. What might be the overall annual treatment cost for all jurisdictions?
    d. What factors would trigger a renegotiation of further discussion?
    e. How can we involve patients in the discussion?
3) **Agree to Continuous Learning:** This would apply to the disease and the available treatment(s):
    a. Assess how partners can collaborate to generate data and real word evidence (RWE) that shows how patients respond to / benefit from treatment?
    b. Set specific milestones for each patient: what improvements do we want to see?
4) **Agree to Continue What's Working:** Patients who are compliant and achieve milestones should have the opportunity to continue treatment. The partners can set pre-determined milestones to address "value": who is benefitting, how they are benefitting, and whether "cost" should be revisited
5) **Agree to Share Risk:** Managed access agreements should contemplate and agree upon appropriate risk sharing between payers and innovators if patients do not achieve expected treatment milestones. They should also recognize that patients have a responsibility to help ensure resources are having an impact on health outcomes.

At the level of individual submissions, manufacturers would be willing to contribute data from their patient support programs and provide international data regarding a specific therapy. Several RAREi members have experience with international tailored models for assessment and funding purposes. We would welcome the opportunity to help inform the EDRD WG about our experiences.

4. Please provide your perspective on real world evidence (RWE) and how it could be incorporated into the current processes.

The use of RWE is vital to the proper evaluation of rare disease therapies. The standard assessment methodologies, which employ a population-based approach, are generally ill-suited for these diseases.

To clarify, not every product would require reliance on RWE, but it definitely should be an option when sufficient clinical trial data is not available. It should be used to fill clinical gaps and/or increase certainty that the right patient is receiving the right treatment. However, RAREi

recognizes that RWE is not a replacement or proxy for robust clinical trial evidence when it is possible to produce it.

Also, HTA reviewers and public plan decision-makers must understand that manufacturers may not be in a position to respond positively to every request for RWE given that research and development priorities are developed at a global level, and domestic activities must be consistent with those international imperatives. As such, the development of an RWE plan for a given product should be the product of collaborative dialogue and agreement.

In order to support a more customized process, a national RWE framework should be developed that sets out expectations of industry and product sponsors as well as other health information stewards. High-quality sources of data should also be set out in the framework, such as administrative databases, patient registries that have been established at the national or regional level, patient support programs, and international registries, along with processes for sharing and maintaining patient privacy and confidentiality. Ultimately, such a framework would ensure that all parties (manufacturers, the regulator, health technology assessment bodies, negotiators, public drug plans, and any other entity that may contribute or rely on RWE) understand their respective roles and responsibilities.

In an effort to better facilitate the use of RWE, rare disease innovators are prepared to contribute real world data, including data gathered by patient support programs and international real world experience. We would also be pleased to discuss a role for manufacturers in setting up new patient registries related to specific therapies.

5. What challenges and/or opportunities do you see in obtaining and using RWE?

RAREi broadly supports the use of RWE and views it as an important element in moving towards a more customized process for the review and evaluation of rare disease therapies. Ultimately, the collection of RWE should be embedded in a conditional approval process to facilitate evaluation and funding decisions. The types of RWE required and the processes involved in collecting and assessing it could be addressed at a pre-submission consultation meeting with representatives from across the regulatory and reimbursement process.

Wide-ranging collaboration involving the full range of affected stakeholders would be key to the successful development of an effective national RWE framework and supporting infrastructure. The framework will need to address methodologies for collecting and assessing RWE. In the early phases, flexibility about the results expected from sources of RWE based on what is currently available would also be important.

6. What is your perspective on having a national review panel to review patient cases? How do you believe this will impact access to EDRDs?

The inclusion of a national review panel to review individual patient cases and determine whether that specific patient should be eligible for a given rare disease therapy according to pre-established reimbursement criteria holds great promise as a means to improve patient

access to appropriate therapies to address their unmet needs. RAREi is very supportive of this concept if organized appropriately.

Reimbursement criteria, including start and stop criteria and criteria of importance to patients, should be developed in a collaborative fashion via input from HTA reviewers, expert committee members, clinicians with disease-specific expertise, manufacturers and patients. The panels should include clinicians and patients from Canada or another jurisdiction who have experience with the therapy.

If clinical panels are created, they should be relied upon to determine the eligibility of individual patients against the pre-established criteria. However, patients should be offered the option of having the panel's determination appealed to ensure that their circumstances were accurately understood and appropriately considered. In addition, the process should be designed so as to limit the administrative burden on treating physicians who may be reluctant to participate if it takes away from their ability to effectively manage their practices.

Please note that existing provincial opportunities for exceptional access consideration (such as Quebec's *patient d'exception*) should be retained as an important alternative access option.

Overall, for the panels to work optimally, there would need to be a mechanism in place to deal with urgent cases (for example, 24-hour response timeframes and clear decision-making capacity), an appeal mechanism and minimal delays following the panel deliberations for patients to get access to these life-altering therapies. If these issues are addressed, it could be a very effective mechanism to address some of the current delays in patient access.

7. In considering the proposed process, have we missed anything?

The proposed supplemental process is a considered way forward. However, it should be noted that the proposal does not address how the funding of rare disease treatments would be organized. RAREi recommends the development of a separate public drug plan for rare diseases, supported by its own funding, formulary, review and appeal process. The ongoing dialogue about national pharmacare – and its potential implementation – may provide an opportunity to create a specific system for rare disease therapies that builds on the working group's proposal.

This submission has already addressed RAREi's feedback regarding specific elements of the proposal that we feel are essential to ensure that the objective of improving patient access to rare disease therapies is met.

In particular, we have shared with the working group our perspective on specific limitations of the existing medication review processes, such as the need for a definition of rare disease and the requirements for clarity regarding the recently-announced priority review changes proposed by Health Canada and their implications for the proposed process. We also noted the importance of a pre-submission alignment meeting at which each participating review agency can articulate potential areas of uncertainty and work collaboratively with the manufacturer to address them, as well as the importance of disease-specific expertise at the table when

evaluating rare diseases, which are often poorly understood. Finally, we detailed how this process can support immediate patient access to rare disease therapies.

We bring to the discussion constructive ideas to pave a path forward for improved access to rare disease therapies for Canadians that balance our concerns as manufacturers with those of regulatory and reimbursement agencies. We look forward to continuing the dialogue and, together, developing a collaborative approach to further refining the proposal and related frameworks and infrastructure.