August 10, 2020

Suzanne McGurn
President and CEO
Canadian Agency for Drugs and Technologies in Health (CADTH)
865 Carling Ave., Suite 600
Ottawa, ON K1S 5S8

Dear Ms McGurn,

On behalf of RAREi, the Canadian Forum for Rare Disease Innovators, I am writing to offer the group's input into CADTH's current consultations related to recently proposed revisions to CADTH's drug reimbursement review processes procedures as outlined in *CADTH Pharmaceutical Review Update – Issue 16*.

As a starting point, please note RAREi's surprise regarding CADTH's decision to limit feedback through a restrictive and highly structured survey instrument which confines the opportunity for interested stakeholders to offer higher-level and/or more general input regarding the proposals outlined. While clear that the survey will reduce CADTH staff's workload and administrative burden in collecting stakeholder feedback, it makes it challenging for commentators to input fully. To clarify, RAREi has no issue with the use of a survey instrument to collect input on certain specific questions. However, such a survey could have been organized in such a way as to permit stakeholders to offer comments on broader themes and questions than just the specific procedural changes of interest to CADTH.

With that in mind, RAREi wishes to restate its concerns with the continued lack of options within CADTH's review processes to address the special needs of rare disease treatments. Nothing in the current CADTH proposal improves the situation for rare disease treatment review and RAREi believes that is a significant oversight on CADTH's part.

RAREi has noted in previous communications with CADTH that it strongly believes that none of the elements of Canada's existing pharmaceutical review process (including regulatory review, pricing determinations, health technology assessment, product negotiation or reimbursement) are appropriately organized to address the unique requirements of rare disease medication development or to facilitate access to needed treatments by patients.

In the context of CADTH reviews, RAREi acknowledges that CADTH has made public commitments to accommodate the evidence available to support reviews of orphan products within its existing review processes, but despite that expression of good intentions, it has not altered its basic approach to evaluating medicines in a manner that indicates a full appreciation for the distinctive nature of the rare disease development process, and the need for a fundamentally different approach to comparative cost-effectiveness reviews for such treatments. RAREi wonders why it has been possible for CADTH to introduce distinct review processes for cell and gene therapies and for blood and plasma products, but it has resisted the same consideration for rare disease treatments.

This is especially confusing in the context of a published academic analysis prepared by CADTH staff of the impact of relying on the current health technology assessment (HTA) process to support public reimbursement of rare disease treatments. The study found that applying the same HTA decision-making framework to these

medicines, “might have contributed to the higher rate of negative reimbursement recommendations made...” and that, at least ultra-rare disease treatments, “could be viewed as distinct category from an HTA perspective.”[1]

Moreover, CADTH was involved directly in the development of the provincial/territorial Expensive Drugs for Rare Disease[2] (EDRD) Working Group’s proposed supplementary reimbursement review process for complex/specialty medicines which was intended to create a robust alternative method for considering public funding of new rare disease treatments. The proposed process acknowledged that current HTA processes are ill-suited for consideration of rare disease treatments and need to be modified in order to account for the differences in the way they are developed. To clarify, RAREi is not endorsing the proposed EDRD framework, which we hope will continue evolve in the context of a broad multi-stakeholder dialogue, but RAREi agrees that the current HTA methodologies are not well-suited to proper evaluation of rare disease treatments.

RAREi has consistently expressed the need for a distinct national review and approval process, public funding mechanism and reimbursement framework customized to account for the particular challenges that orphan products face when innovators attempt to make them available to Canadian patients. The lack of a distinct rare disease treatment review and approval framework puts Canadian patients at a comparative disadvantage globally since Canada is one of the few developed countries that does not have a comprehensive rare disease policy framework. Ultimately, this gap limits access to life-changing treatments for Canadians affected by these diseases.

RAREi calls on CADTH to work collaboratively with the Canadian rare disease community to create a separate and distinct rare disease review process which, among other modifications, would provide for:

- Early engagement between HTA reviewers and innovators to determine how best to assess the medication in light of the available evidence
- Enhanced input from disease-specific clinical experts
- Practical expectations regarding pharmacoeconomic evidence and
- The joint development of clinical criteria by HTA reviewers and expert committee members, disease-specific clinical experts (Canadian or international) and the relevant innovator.

Regarding CADTH’s proposal to enhance transparency by making all elements of a sponsor’s submission public, RAREi wishes to note that it acknowledges the importance of transparency, and appreciates CADTH’s efforts in this regard. However, RAREi believes that a limited measure of confidentiality within submissions is appropriate, and in some cases, necessary.

While true that CADTH has moved from its original position in this regard, and is now proposing that a limited opportunity would be available for sponsors to seek redactions, RAREi is concerned that the draft exemption criteria are too narrow, especially for rare disease innovators. That is because the overall amount of data available to support orphan product approvals can be limited compared to the material that is available in the context of diseases intended for larger patient populations. Since much of the data collected by rare disease innovators are based on creative study designs and proprietary work, there needs to be greater flexibility built

[1] Richter et al. *Characteristics of drugs for ultra-rare diseases versus drugs for other rare diseases in HTA submissions made to the CADTH CDR*, Orphanet Journal of Rare Diseases (2018) 13:15.

[2] Please note that RAREi has noted its objections to the pejorative description of these medications as “Expensive” previously. It must be stressed that rare disease medications have relatively low budget impacts and that characterization does not account for the societal value that can be found through reliance in such treatments.

into the redaction review process to allow for greater scope than CADTH proposes. If that is not done, this proposal would add yet another barrier to the already burdensome process of orphan treatment development and approval in Canada.

Another issue of significant and, lately, much more urgent concern, is the manner in which CADTH calculates the incremental cost-effectiveness ratios (ICERs) based on reanalyses of the numbers presented by sponsors in their submissions. To be clear, this has been a longstanding concern by sponsors, but in the context of the Patented Medicine Prices Review Board's (PMPRB's) forthcoming reliance on CADTH ICERs to assist it in setting maximum selling prices for new patented medicines in Canada, the concern has become much more acute.

A recent analysis conducted for RAREi by Patient Access Solutions indicated that that the majority of CADTH's re-analyses result in ICERs that are 2- to 4-fold higher than those submitted to CADTH by sponsors. The revised ICERs are altered by CADTH for a variety of reasons, including differences in assumptions, disagreements about the population likely to be served by the medication or the appropriate comparators and alternative views about the proper dosing, among others. Significantly, CADTH's recalculated ICERs are not subject to any external correction, oversight or validation.

RAREi's position is that the changes driving the recalculations often do not reflect clinical realities or current medical practice. Significantly, PMPRB's intention is to reduce ICERs for multiple indications, and widely varying ranges for a given medicine, to a single point estimate for all Canadian markets. Given the potential new market impact of ICERs, the significant inadequacies of CADTH's current approach to recalculating ICERs must be addressed. Unfortunately, the current proposals do not do so.

We hope you understand the need for this letter since most of the feedback we have outlined above could not be addressed in the context of the survey questions that were posed by CADTH as part of its consultation. However, in order to ensure that RAREi's feedback on matters that are relevant to the questions posed is included, RAREi also has submitted some of its views through that mechanism.

In addition, please note that RAREi endorses the more comprehensive submissions that have been prepared by Innovative Medicines Canada and BIOTECanada. We ask that you consider that input as representative of RAREi's views as well. I hope this additional input will be helpful in contributing to the innovative industry's input into your consultations. Thank you for the opportunity to share RAREI's perspectives.

Please note too, that RAREi stands ready to participate in further dialogue and address any questions that may arise upon your review of RAREi's input. The members look forward to working with you to improve the review process and ensure rapid access for Canadian rare disease patients to new medical innovations.

Please do not hesitate to contact the undersigned if you have any questions.

Best regards,

Bob McLay
Chair
RAREi – The Canadian Forum for Rare Disease Innovators

RAREi Responses to CADTH Survey Questions

Q - How could the final recommendation document be improved? Is there content that should be added, removed, or presented in a different way?

RAREi believes that it is inappropriate for CADTH to recalculate sponsor-submitted incremental cost-effectiveness ratios (ICERs) in isolation. Given that there is no opportunity for anybody external to CADTH to review, correct or validate the CADTH reanalyses, the final recommendation should include the sponsor-submitted ICERs, as well as a detailed explanation as to how CADTH reviewers arrived at the revised ICERs and what calculations were used to arrive at the altered numbers.

Q - Does your organization support increased transparency in CADTH's reports and recommendations?

RAREi acknowledges the importance of transparency, and appreciates CADTH's efforts in this regard. However, RAREi believes that a limited measure of confidentiality within submissions is appropriate, and in some cases, necessary.

Q - Does your organization have any comments or concerns related to CADTH's proposal for information that would be considered disclosable by CADTH?

Broadly speaking, RAREi would like sponsors to have the opportunity to protect any element of a sponsor's submission that is not already public and/or which the company considers proprietary or confidential for competitive reasons.

At a minimum, RAREi suggests that CADTH implement confidentiality policies related to sponsor submissions that are largely similar to Health Canada's approach in this regard. In particular, RAREi wants CADTH to ensure that data that is or planned to be subject to peer review in the context of publication in an academic journal should not be considered disclosable.

While RAREi appreciates that this may impose additional resource requirements on CADTH staff, it believes that is the obligation of any third-party evaluator which relies on sponsor-submitted data to protect that data to the best of its ability.

Q - Does your organization have any comments or concerns related to CADTH's proposed process for redacting confidential information from CADTH documents?

RAREi recognizes that CADTH is proposing that a limited opportunity would be available for sponsors to seek redactions. However, RAREi is concerned that the draft exemption criteria are too narrow, especially for rare disease innovators. That is because the overall amount of data available to support orphan product approvals can be limited compared to the material that is available in the context of diseases intended for larger patient populations. Since much of the data collected by rare disease innovators are based on creative study designs and proprietary work, there needs to be greater flexibility built into the redaction review process to allow for greater scope than CADTH proposes.