pCPA Temporary Access Process:
Innovative Medicines Industry Consultation Response

August 18, 2023

Innovative Medicines Canada (IMC) and BIOTECanada are the primary associations representing the innovative medicines and vaccines industry in Canada. Thank you for the opportunity to provide feedback to the pan-Canadian Pharmaceutical Alliance (pCPA) Temporary Access Process (pTAP) proposals.

We have engaged in detailed discussions with CADTH on its Time Limited Recommendation (TLR) framework from which the present pTAP proposal originates. Many of the key themes, questions, and suggestions in relation to the TLR document are consistent and remain relevant in the downstream pTAP context. Our written feedback to CADTH provided in May 2023 is attached as appendix and should be reviewed as a companion to this submission.

It is important to note that CADTH has not yet finalized its TLR framework and many of the parameters of that document such as issues of scope and timing criteria will have bearing on the uptake of pTAP and the ultimate utility of the TLR/pTAP pathway. Furthermore, it should also be noted that impact of Health Canada's Agile Licensing reforms, and specifically the future status of the Notice of Compliance with Conditions (NOC/C) policy, is unclear at present.

IMC and BIOTECanada recognize the efforts toward process innovation inherent in the TLR/pTAP initiative. We encourage pCPA and CADTH to think more boldly about how this pathway will evolve to provide faster access for patients, sustainability for health system managers, and opportunities for Canada to improve its life science performance and international launch sequencing.

Our industry supports reimbursement solutions that promote appropriate resource allocation and implementing new pathways to manage the entry of innovative products earlier in the product lifecycle with ongoing evidence generation programs. We have consistently advocated for coverage with evidence development and the TLR/pTAP is an incremental first step that can provide a platform for future advancement towards more agile payer models. However, it is important to note that the pCPA exclusively manages public reimbursement and therefore the pTAP must remain restricted to public plan considerations.

Tangible acceleration of patient access needed under TLR/pTAP

As a primary consideration, pTAP represents an opportunity to identify tangible measures to accelerate product files in the earlier stages of the reimbursement process. For example, manufacturers with files meeting the criteria for TLR should start discussing the initial pTAP provisions in parallel with CADTH review, or at a minimum, should eliminate the significant delays between CADTH completion and pCPA Letter of Engagement (e.g., start pTAP discussions at the initiation rather than at the

finalization of the CADTH TLR review). Unless such efficiencies are incorporated, or other acceleration provisions are implemented it is unclear if there are any access timeline benefits associated with the pTAP process.

We encourage pCPA to identify specific provisions to accelerate access, namely the opportunity to commence a pTAP negotiation sooner and consider conducting this process in parallel with CADTH TLR review. While the TLR/pTAP pathway is not intended to alter provincial legal frameworks regarding product listing agreements, we encourage public payers who have committed to a pTAP negotiation to implement all pCPA Letters of Intent within a 30-day timeframe.

pTAP as a framework for negotiations

We recognize the pTAP is a framework to conduct multiple negotiations during the product lifecycle. This would appear to involve a negotiation at product introduction based on an incomplete Health Technology Assessment (HTA), due to the emergent nature of the science and available evidence at time of launch. A follow-up negotiation would subsequently be conducted once the clinical information required by Health Canada has been advanced or finalized.

In some cases, the key negotiation parameters (price, indication, patient sub-population, anticipated budget impact, and post-funding patient management) could be addressed during the first negotiation, and greater efficiency can be achieved through relatively minor adjustments during the second negotiation. Where appropriate, there could be value in addressing key parameters in the first negotiation for different potential Phase III data outcomes scenarios.

For products where evidence is less certain at launch, a more comprehensive secondary negotiation may be required. Negotiation requirements will likely differ according to product-specific considerations. The evidence required by CADTH may be different from that required by Health Canada. Therefore, a flexible and fit-for-purpose process will be most beneficial for all parties.

For a TLR submitted product, the pCPA has stated that it will determine whether or not a negotiated agreement will be pursued. In order to ensure predictability for manufacturers, the conditions by which the pCPA will enter or not enter into a pTAP, including the scope of products and criteria, need to be transparent and reasons need to be provided to the manufacturer.

Flexible guidelines rather than binding criteria

IMC and BIOTECanada have previously noted a number of challenges that could arise from excessively binding criteria that may not be possible to address in every case (e.g., three-year study completion criteria; re-submission timelines: please see the attached TLR submission). We encourage CADTH and pCPA to clarify that timelines and other provisions currently noted as criteria, are instead more general guidance or notional targets. We understand that CADTH has selected the three-year timeframe with the intent of making this pathway more efficient and attractive for jurisdictions given the typical three-year product listing agreement cycle. While this timeframe may be appropriate in some circumstances, the period should be flexible to account for product-specific timelines and evidence requirements.

Timelines should be determined on a case-by-case basis and flexibility should be built into the process to manage unanticipated circumstances.

Agreement extension provisions for unanticipated circumstances

pTAP Letters of Intent could include provisions for the possible extension or renewal of the original term where there is mutual agreement. This may be helpful in situations where clinical data is delayed (e.g., due to above-market factors such as trial completion delays) or when follow-on regulatory or HTA reviews take more time than originally anticipated. For example, pTAP agreements could be extended for 12 to 18 months in the event that more time is needed beyond the initial temporary access period.

Scope should include products with real-world evidence plans

IMC and BIOTECanada recognize that the TLR and pTAP initiatives have been designed to address a small number of products with planned phase III clinical trials. While we understand the rationale for starting with a small group of products to achieve early successes, this objective can still be achieved by including products where manufacturers propose plans for decision-grade real-world evidence (RWE).

When coupled with innovative payer agreements (outcomes-based agreements, managed entry, coverage with evidence development), RWE holds considerable promise to help governments strategically manage the entry of new medicines. They will also help to address protracted reimbursement timelines by allowing governments to provide earlier access with ongoing development of real-world outcome data and subsequent assessment of a medicine's real-world performance. This may be particularly relevant for pTAP products where there may be a higher degree of unmet medical need and where greater uncertainty of evidence exists, for example, due to study limitations associated with small patient populations for rare diseases.

CADTH and manufacturers have engaged for years on RWE and CADTH recently finalized an RWE Guidance Document. It would be a missed opportunity if products with RWE or where a phase III trial is not possible or ethical (which is often the case for rare disease medicines) were excluded from pTAP consideration. We understand from discussions with pCPA that it will defer to CADTH regarding evidence criteria. In the course of these discussions, pCPA did not seem generally opposed to alternative scope possibilities. Therefore, we reiterate industry's position on scope within the attached TLR submission and hope to address these scope issues directly with CADTH.

No automatic application of the CADTH-recommended prices

The language in the pTAP proposal on "prices set according to established cost-effectiveness" is open to different interpretations. There is often considerable disagreement between CADTH reviewers and manufacturers regarding cost-effectiveness analysis. Cost-effectiveness analysis is particularly questionable in situations where evidence is uncertain at the time of product introduction (i.e.,., particularly relevant for those products subject to ongoing evidence generation under TLR/pTAP).

CADTH's current drug program review often makes unrealistic price reduction recommendations (e.g., recommendations to lower prices by 90% or even 100%), which are routinely used as the starting point for pCPA negotiation processes. We are not supportive of price reduction recommendations based on a single incremental cost effectiveness ratio (ICER) point estimate and encourage a return to a more nuanced approach where uncertainty is reflected within an *ICER range* for the purposes of informing pCPA negotiations. As such, CADTH-recommended price reductions will require further discussion following the time-limited recommendation, and negotiations on a product-specific basis will be needed.

This issue also emphasizes the need for the pTAP process to have the appropriate level of flexibility to meet the complex needs of these negotiation processes without slowing them down. To this end, industry does not recommend a process similar to the Targeted Negotiation Process, (TNP) which is often experienced by manufacturers as inflexible and one sided, and which would further limit the potential utility of the pTAP.

These negotiations can be informed by budget impact analysis and the TLR recommendation. For greater certainty, we are supportive of achieving sustainability through negotiations. However, any provision mandating the automatic adoption of the CADTH's recommended price as the established "cost-effective" price as a condition for pTAP would undermine the viability of the new pathway.

As discussed in our May 2023 TLR submission, CADTH and pCPA should consider scenarios where economic considerations during the initial temporary access period could be informed by other inputs, such as current Budget Impact Analysis (BIA) submissions. This suggestion is contingent upon no major changes to the current BIA, given that BIA template discussions may be forthcoming in 2023-24.

Balanced approach to risk sharing

While risk sharing is an important element of the pTAP, the risks assumed by each party are not directly addressed in the proposal. Management of ongoing patient access following a delist or no-agreement scenario (e.g. who pays for ongoing access to care in the event of a decision not to fund or negotiate, or an exceptional circumstance where phase III trials are not met for some indications) will be most feasibly addressed through product-specific discussions and flexibility. Negotiated protocol for patient continuity or alternative measures such as the consideration of RWE generated during the temporary period can help to ensure an equitable balance of risk between manufacturers and payers, and ensure a patient-centric approach.

Ongoing dialogue and multi-stakeholder engagement following adoption

IMC and BIOTECanada thank pCPA and the jurisdictions for the opportunity to comment and have made best efforts to provide initial comments and address key considerations in response to an accelerated summer consultation window. It will be important for all stakeholders to be involved in the monitoring, assessment, discussion, and evolution of the process on an ongoing basis and following some experience with the TLR/pTAP. We therefore recommend that continuous stakeholder consultations occur at appropriate intervals during and following the introduction of the pTAP.

The TLR and pTAP framework have the potential to increase access and availability to new treatments , but it will require goodwill, flexibility and innovation from HTA agencies, public payers, industry and other stakeholders to realize its potential. IMC and BIOTECanada look forward to contributing to this important initiative for Canadian patients.

Attachment (IMC/BIOTECanada TLR submission)

Time-Limited Recommendations:
Charting a path to Innovative HTA Approaches

May 1, 2023

Innovative Medicines Canada and BIOTECanada are the primary associations representing the biopharmaceutical and vaccines industry in Canada. We thank CADTH for the opportunity to comment on its consultation regarding the process for time-limited recommendations (TLRs). This submission is intended as a starting point for a further dialogue prior to finalizing the policy and we acknowledge CADTH's offer to engage directly on this important topic.

Incremental first step, pending appropriate scope and implementation details

Innovative Medicines Canada and BIOTECanada have long supported health technology assessment (HTA) processes in Canada that are agile, responsive, and consider the evolution of evidence through a medicine's lifecycle. The present consultation provides an incremental first step in the direction of addressing uncertainty that may exist at the time of a medicine's launch.

A key objective of the TLR framework should be to enable early patient access to therapies with promising value. We encourage CADTH to think more boldly regarding the calibration of its HTA review process to facilitate Coverage with Evidence Development, outcomes-based or other forms of innovative payer agreements that are enabled by real-world evidence (RWE).

While the proposed scope has been targeted to Health Canada notice of compliance with conditions (NOC/c) products with plans for a phase III clinical trial, it ultimately could be broadened to help facilitate innovative approaches and more timely patient access to a range of innovative medicines that could benefit from such an HTA process. For example, this includes drugs for rare diseases, including rare cancers, which cannot always conduct phase III clinical trials for reasons such as the feasibility of studying small patient populations or for ethical reasons, but could benefit greatly from evidence generated in the real-world and built on a foundation of well conducted observational research.

Recalibration following Health Canada's possible implementation of Agile Regulations

Based on our analysis of publicly available sources, approximately 14.4% of files receive conditional approval under the current Health Canada NOC/c system (see table below). This is expected to grow under Health Canada's proposed Agile Licensing framework and associated Terms and Conditions (T&C) system that is currently subject to consultation. The scope of medicines impacted by T&Cs remains unclear and subject to policy finalization. In general, if T&Cs are imposed post-launch, they should not trigger CADTH re-reviews.

A review and recalibration of CADTH's TLR policy will therefore be required after Health Canada finalizes its regulatory amendments and related guidance documents and following a reasonable period of operation under the new system. This review may help to manage possible downstream implications of more numerous CADTH reviews. In summary, we support piloting TLRs with options to revise at a later date.

Downstream impacts will be critical to monitor, communicate, and manage

Duplicating HTA review for up to 14% of files (or possibly more following the aforementioned regulatory changes) could have significant downstream implications at the pan-Canadian Pharmaceutical Alliance (pCPA) negotiation and F/P/T payer levels.

There are ongoing questions regarding how TLRs may interact or compound other forms of HTA re-review such as optimal use (therapeutic reviews), oncology algorithms, non-sponsored reviews and possible Post-Market Drug Evaluation (PMDE) related efforts. These processes all raise interrelated downstream implementation questions, and in some cases, may trigger complex secondary negotiations. There remain outstanding questions regarding how the pCPA and payers may implement TLRs including implications for negotiations and what their capacity will be to provide timely access to medicines with a positive TLR.

As review system complexity continues to accelerate, downstream and implementation considerations must be carefully monitored over time to ensure efficient resource allocation and ensure that processes are streamlined across these different workstreams that implicate reassessments and possible renegotiation. TLRs will not be necessary for all NOC/c, and/or future T&C products. To proactively manage review volume, TLRs should be explored only when there is a clear rationale related to significant additional evidence.

The success of this initiative hinges on engaged, real-time dialogue, between CADTH, industry, pCPA and other stakeholders. We recommend that CADTH, in consultation with industry and other stakeholders, evaluate this new policy as it is implemented within a pre-defined number of files, to identify opportunities for process improvement, and to assess intended versus actual impacts.

Coordination with Quebec's INESSS should also be explored for shared learnings and possible efficiencies given similar issues are at currently at play in that system.

Is pharmacoeconomic analysis always needed at launch?

We would encourage CADTH to consider possible scenarios where, due to uncertainty at time of launch, an economic analysis for TLRs could be delayed until later in the product lifecycle when more evidence is available (i.e., when a more reflective pharmacoeconomic analysis can be conducted). This may be particularly relevant for drugs for rare diseases which struggle under current HTA models and could benefit from innovative alternatives to HTA-at-launch.

In such a scenario, budget impact analysis could still provide payers with insights on the estimated financial implications and enough information to proceed with timely listing negotiations, which can be refined later based on evidence development.

A fit for purpose approach to pharmacoeconomic analyses

Some efficiencies within the proposals may help to proactively address the downstream issues identified above. Efficiency can be achieved through a differentiated and context-specific approach to economic evidence that is established through early dialogue with the manufacturer.[1]

For example, some Health Canada evidence conditions may involve relatively straightforward issues that will not have implications for comparative cost-effectiveness. In cases where a pending phase III trial or other conditions will not have a bearing on pharmacoeconomic issues, CADTH should not require the updating and re-review of the economic model. For these submissions, pharmacoeconomic evaluation may be conducted at launch and may not require a full economic re-evaluation.

The TLR process document could account for this flexibility by clarifying that that not all TLRs will require two full pharmacoeconomic reviews.

In summary, the TLR process should be flexible according to the situation. Sometimes it will make sense to forgo pharmacoeconomics at launch and budget impact can suffice to inform pCPA negotiations (see above). At other times where Health Canada conditions do not have implications for payers, a pharmacoeconomics review can be conducted at launch and conditions can be lifted without needing to trigger another full pharmacoeconomic assessment, and possible downstream negotiations.

Practical issues

There are a number of practical issues and questions that will require further detailed discussion and refinement:

- Clinical trials are not always feasible within a 3-year time frame.
- We foresee likely issues with submissions for reassessment within 180 days following a trial completion – due to the time required to analyze and synthesize the data at a global level and then compile into a local submission meeting CADTH's requirements (potentially even a re-

[1] To achieve common agreement on data that will be generated to fulfil the TLR requirements, manufacturers and CADTH can work together to set expectations for how uncertainty will be captured in the TLR. This can include robust, transparent pre-submission meetings with sponsors to enable early alignment on data requirements, to inform submission preparation, facilitate reviews and consider downstream implications.

structured PE model), this will not be feasible in many circumstances and should be reflected as an aspirational target.[2]

- Specific definitions for trial "completion" also require more clarity (e.g., can CADTH confirm this refers to trial publication?).
- Are files with an NOC/c that do not have a confirmatory phase III randomized control trial (RCT) out of scope and will they continue to be reviewed under the status quo process? If so, could TLRs be extended to other applications that may not have a phase III RCT?
- What if Phase II and Phase III trial populations differ (e.g., differ with each other and/or differ with the reimbursement indication population, as discussed below).
- Filing requirements in relation to identified timeframes should be discussed further - how will files be managed that have an NOC/c with a confirmatory phase III RCT that will not be completed within the identified timeframe?
- If Health Canada accepts surrogate endpoints as part of the qualifying notice, will CADTH and payers also accept this? CADTH should clarify how surrogate endpoints will be addressed in its reviews.
- What are the impacts to patient organizations and clinicians regarding workload?
- Although it is anticipated that failed Phase III trial or "do not reimburse" recommendations upon reassessment would be the exception rather than the rule, there should be an agreed framework for how payers and manufacturers manage these situations.

The aforementioned issues and questions are non-exhaustive and would benefit from additional technical and downstream discussions.

TLR as an optional process and not a deliberative factor in-of-itself

The TLR process must remain optional at the manufacturer's discretion. There are many reasons a company may decide not to opt-in to the TLR stream. A decision not to pursue a TLR should not inform expert committee decision-making within the regular reimbursement review stream for that product (e.g., standard review recommendations should not be impacted by the absence of a TLR).

Given limited resources, it would be helpful for CADTH to clarify how TLR reassessments may be prioritized among other review types at expert committee meetings.

TLRs should evaluate uncertainties specific to HTA and downstream needs

The questions regarding clinical uncertainties posed by regulators are not always the same questions posed by CADTH and payers. Different subpopulations or treatment questions may be under study. Phase III clinical trials that are pending at the time of NOC/c may address some regulatory questions, but will not always address HTA or payer questions. The requirements imposed by Health Canada to lift

[2] We note that the timeline for removal of conditions is negotiated case-by-case with Health Canada; there is no standard requirement. Similarly, the timeline to make a re-assessment submission should be agreed case-by-case with CADTH, to align with what is agreed with Health Canada.

NOC conditions cannot be assumed to be material to a price re-negotiation and may often be irrelevant to reimbursement.

As such, a flexible approach to TLRs must be adopted. Ideally, companies could apply for TLRs beyond the regulatory scope proposed, for example, TLRs to help facilitate coverage with evidence development. TLRs could be a path for innovative products, where uncertainty may still exist with phase III studies, yet their value could be demonstrated via established registry or other RWE platform (where applicable).

Consistent protections for confidential business information

The innovative medicines industry is supportive of enhancing transparency of HTA processes to the extent that there remain opportunities for the protection of sensitive confidential business information (CBI). We are also committed to limiting the volume of redactable information to material that is truly sensitive in nature.

As such, protections for CBI must be upheld under the TLR process. The same protections and redaction opportunities afforded to regular CADTH reviews should also apply for TLRs.

While we believe this is CADTH's intent, we reiterate that only material on evidence generation plans that is already disclosed in Health Canada's documents should be subject to a no-redaction policy. For clarity, once that evidence generation plan is executed, there may be CBI contained in the evidence generated that will still require opportunities for redaction.

Fees

We note that the proposal effectively doubles the fees for products undergoing the TLR process. We also note that additional workload will be created for the manufacturer but there may be reviewer economies for situations where the review material would be essentially similar to the initial submission.

While views on fees may differ somewhat across the industry, we are not necessarily opposed to some incremental fees. However, CADTH should explore alternatives for reduced fee options where review workload for the initial or second review within the TLR may be limited (e.g., simple lifting of conditions based on a confirmatory study). One alternative could be that instead of having a fixed fee for the re-assessment submission, the fee would be determined following the receipt of the submission, based on the scale of the review, similar to what is currently done for the CADTH Scientific Advice fees.

Conclusion

Thank you for reviewing this input and for CADTH's willingness to engage in more detailed future discussions. Many questions relate to broader deliberative and downstream issues, and we recommend

that CADTH re-engage on a comprehensive evaluation and consultation of its deliberative processes, including decision-making transparency and HTA responsiveness. This will help the industry and CADTH collectively ensure that we are addressing patient and payer needs as more complex and specialized therapies promising improved patient outcomes are developed and submitted for review.

Appendix – Analysis of Historical NOC/c

	NOC	NOC/c	Total
2015	**30**	**7**	**37**
2016	**30**	**7**	**37**
2017	**28**	**6**	**34**
2018	**39**	**1**	**40**
2019	**27**	**5**	**32**
2020	**32**	**3**	**35**
2021	**32**	**11**	**43**
2022	**40**	**3**	**43**
2023	**2**	**1**	**3**
	260	44	304

= 14.4% NOC/c as a % of Total

Source: Health Canada's Notice of Compliance database. Search criteria was restricted to product types "prescription pharmaceuticals" and "biologics", and submissions class as "NAS" or "Priority-NAS". April 2023.