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SUBMISSION FROM PDCI MARKET ACCESS TO CADTH:

Stakeholder Feedback on CADTH's Pharmaceutical Review Consultations

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RESPONSE FROM PDCI MARKET ACCESS

1. Proposal to Enhance Transparency of CADTH's Review Reports and Recommendations	
1.	Do you support the proposal objective? Please provide your rationale.
	Feedback In principle, PDCI supports further enhancing the transparency of health technology review processes, including CADTH's. However, there must be protection (non-disclosure) of confidential information submitted by manufacturers. Disclosure of confidential information may cause harm: it may adversely affect the privacy of patient health information; it could directly conflict with provisions that must be adhered to by manufacturers relating to the publication of research data. Disclosure of confidential information may wrongly include proprietary commercial information; and it may be prohibited under certain contractual obligations of the manufacturer.
2.	The foreseen benefits with the proposal would be greater accessibility, comprehensiveness, and usefulness of information that would better support the conclusion of a reimbursement recommendation. In your opinion, would there be challenges with implementing this proposal? If so, how could this be managed?
	Feedback There needs to be clarification about what level of disclosure will be undertaken by CADTH. For example, CADTH states "the proposed amendments would allow CADTH to use and disclose information provided by the submitter". True, it would allow using and disclosing information. However, CADTH has not provided clarity, reasoning or other evidence to support why the disclosure of confidential information is actually needed. How does CADTH believe disclosing confidential information would carry greater benefit than harm. Current confidential documents in the regulatory review process include Clinical Study Reports (CSRs), regulatory documents (Common Technical Documents, Reviewer's Report, Clarifaxes, etc.), and Indirect Treatment Comparison Technical Document Reports. These are among documents not disclosed to the general public. There is concern surrounding unpublished information being released in the public domain that can be taken out of context and consequently misinterpreted. For example, issues and questions that may be raised and then addressed in clarifaxes *could* become unintended issues if they are disclosed without broader context known to Health Canada and the manufacturer. The full content of CSRs and other regulatory documents, such as Periodic Safety Update Reports, often include patient-specific reports for which public disclosure may infringe privacy act provisions, the ethical requirements of clinical trials and patient explicit authorizations. For these and many other considerations, manufacturers do not release CSRs; instead, principal investigators draft manuscripts for publication. Disclosure of research findings prior to publication, such as when CADTH is publishing its reports and recommendations, may impact the potential for publication of data in peer reviewed journals. There is mention in the CADTH proposal that its step towards transparency (i.e. disclosing confidential information) aligns with methods currently adopted by Health Canada. However, Health Canada does not publicly post the Reviewer's Reports and only provides them to the manufacturer upon request. This proposal is also not aligned with Health Canada's recently implemented process to release clinical information contained in CSRs (Public Release of Clinical Information); under this process, Health Canada

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	requests that within 60 calendar days the manufacturer submit the de-identified documents with proposed redaction(s). CADTH should align with Health Canada with regards to disclosing information found in CSRs. An option for CADTH to consider as part of its transparency objective is to refer to Health Canada-published documentation; those documents are vetted by the manufacturer for public release and reflect the most up-to-date safety and efficacy perspectives of Health Canada. Additionally, Health Canada allows for masking of sensitive information (Confidential Business Information). CADTH's proposed transparency approach does not appear to accommodate masking/redacting. If implemented, the CADTH transparency proposal would appear to conflict with Health Canada provisions protecting confidentiality. Internationally, CADTH would stand alone in its approach, becoming the first HTA body to disallow redactions of confidential information from published HTA recommendations. Other HTA bodies, including NICE and INESSS, have processes that allow for the redaction of confidential information.
3.	Are there other issues that CADTH should consider in supporting the successful implementation of this proposal?
	Feedback PDCI believes any transparency initiative should be approached with *fair balance.* The level of transparency should be equitable across *all* stakeholders (manufacturers *and* CADTH) in order to promote greater confidence in the CADTH recommendation process. Should CADTH proceed with disclosure of confidential information in its published recommendations, PDCI suggests CADTH should be prepared to disclose publicly the CADTH draft review reports and the manufacturers' submitted written comments about the reports; CADTH should also disclose as fair balance the verbatim written and verbal inputs of clinician experts/panels (rather than the summaries prepared and released by CADTH), the CDEC brief compiled and distributed by CADTH to all CDEC members and drug plans, as well as the meeting minutes of the CDEC deliberations. Importantly, if we compare CADTH's economic evaluation reports to those of other global HTA bodies, there is a noticeable gap between the transparency of the current CADTH approach to economic evaluations and the transparency of published economic evaluations of other HTA bodies such as NICE. Many CADTH economic evaluations include sparse language generally describing changes made to models that are not reproducible even for the manufacturer. In many cases these changes have a substantial impact on reported ICURs and generate substantial uncertainty. These reports may subsequently be used by the pCPA and other parties to inform reimbursement negotiations. Additionally, these economic evaluations may be used by regulatory authorities to establish maximum prices under the proposed PMPRB reforms.

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2.1 Systematic Review of the Literature	
1.	Based on your experience with international health technology agencies that require the submission of a systematic review for single technology assessments, do you have any concerns with CADTH taking this approach?
	Feedback We are aware of Australia's Pharmaceutical Benefits Advisory Committee (PBAC) requiring a systematic review as one component of the Clinical Evaluation but do not have direct experience with this approach. It is our assumption that CADTH has found efficiencies with the tailored review process that can be expanded to the standard review process. However, we question whether the process would ultimately be more efficient and meet CADTH's mandate. It will be important for CADTH to provide clear guidelines and standards for the systematic review. However, while manufacturers may be in a position to assume more responsibility for systematic reviews, PDCI believes there is still a possibility no efficiencies will be gained by CADTH with this process. Consider if CADTH does not agree with the manufacturer's approach in the conduct of the systematic review; conducting a "validating" review through CADTH would defeat the purpose of efficiency gains; if that is the purpose of this CADTH proposal.
2.	What advice would you give CADTH based on your experience with similar requirements in other jurisdictions?
	Feedback Australia's PBAC guidelines provide literature review methods such as search criteria and terms. We suggest that CADTH assess a more collaborative approach where CADTH and the manufacturer jointly develop the search strategy, criteria and terms. CADTH approves the resulting systematic review protocol and the manufacturer conducts the systematic review as per protocol. This suggested approach may require additional resources (personnel and time) up-front but will save time downstream and result in a robust systematic review that meets both manufacturer and CADTH expectations.
3.	How might the requirement to provide a systematic review impact your ability to file submissions on a pre-NOC basis?
	Feedback A systematic review requires time to conduct by knowledgeable and qualified personnel. While manufacturers may accept this responsibility, it could also become a future administrative burden. One possible challenge to this proposed change is the timing of the systematic review, particularly when considering a pre-NOC submission. In the CADTH proposal, it states that CADTH will identify, synthesize, and critically appraise additional relevant evidence from studies that do not meet the systematic review protocol that address important gaps in the evidence. It is unclear what would occur should an additional trial be completed during the CADTH review process that should have been included in the review, and whether CADTH will also need to summarize and appraise this evidence.
4.	What sort of changes should occur in CADTH's pre-submission meeting process in order to accommodate the proposed revisions to the submission and review processes?

	Feedback Longer pre-submission meetings may be required in order to have enough time to discuss the systematic review protocol ahead of the submission. Currently, 1 hour is scheduled for the pre-submission meeting; we propose increasing the length of the meeting by at least another 15 minutes. Since pre-submission meetings can occur up to 12 months prior to submission, there may be a need for the manufacturer to update the systematic review protocol between the pre-submission meeting and the submission filing date, making the proposed process cumbersome. CADTH should consider that additional meetings (at least, teleconferences) between the manufacturer and CADTH staff may be required to ensure that both parties are aligned on the protocol. If CADTH implements its proposed approach for systematic reviews, it should allow for more meetings/touch points following an initial pre-submission meeting.
5.	Should CADTH provide a guidance document guidance on the conduct and reporting (content and structure) of the systematic review?
	Feedback Yes, to help ensure that the appropriate clinical questions are answered, eliminate bias and ensure consistency across submissions. Clarification and guidelines are necessary in order for manufacturers to align with CADTH's evaluation.
6.	Do you foresee any challenges in providing a systematic literature review? Please provide details.
	Feedback In addition to 2.1 feedback #4, it is unclear what would occur if the manufacturer's systematic review does not meet CADTH's standards or expectations. Search strategies, study exclusions, and findings used by the manufacturer for the systematic review may be subject to CADTH critique. CADTH and the manufacturer may have different criteria to define the most relevant outcomes to consider in the review. It will be important to ensure that both the manufacturer and CADTH are aligned with the proposed protocol (see 2.1 feedback # 2 above). There can also be a disproportionate impact on smaller companies who may not have sufficient budget and resources. This may impact their ability to make a submission resulting in a lack of access for patients to their drugs.
7.	Please feel free to comment on any other issues related to the proposed changes.
	Feedback CADTH may deem the manufacturer's review to be biased, discount the systematic review and conduct its own systematic review. This will increase the overall time for CADTH to review the submission and eliminate efficiencies in this process.
2.2 Complete Clinical Study Reports	
1.	Do you support the proposal? Please provide your rationale.

	Feedback Yes, Clinical Study Reports (CSRs) provide the most complete details regarding the design, conducting of, and results of clinical trials that are not found in publications. Currently, CADTH requests the CSRs for most submissions during the review process. However, as noted earlier, CSRs usually contain confidential information that CADTH may disclose unintentionally. Health Canada recently implemented a new process to release clinical information contained in CSRs (Public Release of Clinical Information). CADTH should align with Health Canada with regards to disclosing information found in CSRs.
2.	Do you foresee any challenges in providing the clinical study reports? Please provide details.
	Feedback The CADTH proposal states that final or interim clinical study reports should be provided in full and include both the complete study protocol and analysis plan. CADTH should specify whether all appendices are required or only the complete study protocol and analysis plan. The full CSR can be thousands of pages; extra information under proposed transparency amendments would be subject to disclosure. Please see transparency feedback (section 1, feedback #s 1-3) related to potential study ethics board, patient authorization, privacy and publication implications. In most reviews, the CSR is provided upon request without all related supporting tables (which usually include patient-specific reports). This usually represents a sufficient dataset for making appropriate and informed reimbursement recommendations. Recently, CADTH requests for the full CSR have become more common, but the purpose and need for this extensive dataset is unclear as it pertains to the evaluation of medicines to determine comparative efficacy and cost-effectiveness. CSRs usually contain unpublished and, possibly, confidential data; this is a concern due to CADTH's proposal to enhance transparency of CADTH's review reports and recommendations.
3.	Please feel free to comment on any other issues related to the proposed changes.
	Feedback No other comment.
2.3 Reimbursement Status for Comparators	
1.	Do you support the proposal? Please provide your rationale.
	Feedback Yes, it will help facilitate alignment between the manufacturer and CADTH on the relevant comparators, without adding extensive administrative burden on manufacturers.
2.	Do you foresee any challenges providing information on the reimbursement status of comparators? Please provide details.
	Feedback No major challenges are foreseen.
3.	Do you have any suggestions to improve the proposed template?
	Feedback No, the proposed template is reasonable.

4.	Please feel free to comment on any other issues related to the proposed changes.
	Feedback No other comment at this time.
2.4 Budget Impact Analysis	
1.	Do you support the proposal? Please provide your rationale.

	Feedback
	In principle a pan-Canadian Budget Impact Analysis (BIA) could allow for a clearer picture of expenditures across the country for public coverage – potentially helpful in smaller populations of patients. Yet, CADTH objective here is not entirely clear.
	
	Some considerations as CADTH evaluates this proposal:
	
	• Each CDR-participating jurisdiction currently reviews the impact of the new drug on its own drug plan budget, they do not review the impact of the drug on other jurisdictions' drug plan budgets or on a pan-Canadian basis.
	• As each public drug plan is unique, each BIA is unique
	• There are numerous intricacies that could make implementation challenging:
	  • Different costs, dispensing fees, markup, market share
	  • Slight differences in covered population, comparators
	  • Current guidelines for BIAs are old (from PMPRB)
	
	Another key concern is the potential disclosure of the pan-Canadian BIA and the concomitant release of confidential business information; BIAs are akin to a manufacturer's product sales forecasts.

2.	How might the requirement to provide a budget impact analysis affect your ability to file submissions on a pre-NOC basis?
	Feedback PDCI does not believe this proposal should adversely affect the manufacturer's ability to file a submission on a pre-NOC basis. However, in situations where there are other new drugs with similar potential launch and reimbursement timelines, the pan-Canadian BIA may not accurately reflect the market. If the submission is made pre-NOC and the market changes during CADTH review, CADTH should clarify if the pan-Canadian BIA will need to be updated.
3.	Do you foresee any challenges providing a budget impact analysis as a category 1 requirement? Please provide details.
	Feedback PDCI does not foresee challenges providing a pan-Canadian BIA as a category 1 requirement, however, PDCI questions its purpose (see 2.4 feedback #1).
4.	Please feel free to comment on any other issues related to the proposed changes.
	Feedback No other comment at this time.

3. CADTH's Proposed Reassessment Framework	
1.	Do you support the proposal? Please provide your rationale.
	Feedback In principle, PDCI supports the proposal to monitor and re-evaluate drugs in Canada once they have been funded. It is understood that as the landscape changes, new data and evidence are continually generated. There is, however, the understanding that reassessments will pose uncertainty especially in light of upcoming price policy reformations and these impacts need to be considered in a holistic manner.
2.	Do the proposed reassessment pathways provide enough flexibility to conduct reassessments in an efficient manner?
	Feedback The suggested pathway for reassessment appears to be quite flexible. However, the potential triggers or basis for reassessment seem open to interpretation and, potentially, to bias. The language in the proposal implies that the list of *potential* triggers is non-exhaustive. It is understood that this broad approach is meant to allow numerous scenarios to be applicable for a reassessment and to keep options and opportunities open. However, it needs to be considered that this in turn may raise uncertainty from the perspective of manufacturers. Thus, PDCI recommends there be greater structure surrounding the triggering of reassessments and clarity surrounding the procedure and process upon triggering a reassessment. On the other hand, effectiveness may not be fully achieved as reassessments may put burden on provincial and federal drug plans that may need to revise listings decisions; this would be particularly challenging when product listing agreements (PLAs) are already in effect. Furthermore, there will be a need for prioritization of assessments that may increase administrative burden. The variable interpretation for reassessment triggers could potentially lead to an over-use of the pathway, which also needs to be considered.
3.	Do you foresee any challenges with the proposed reassessment framework?
	Feedback There is potential for over-use of a reassessment pathway if guidelines, procedures and criteria are not fully outlined. It is currently unknown how this increase in work will affect resourcing at CADTH and how this may translate back to manufacturers (i.e., in the form of additional user fees or other internal resource needs). Some of the listed potential triggers for reassessment seem to fall beyond the mandate of CADTH. Expiration of reimbursement agreements and uncertain or potential high budget impact, for example, are issues that should be negotiated with the individual public drug plans and should not require additional HTA assessment. This would be counter to the objective of reducing administrative burden for CADTH under the transparency proposal. The uncertainty for manufacturers as to when a reassessment could be triggered presents an additional challenge. PDCI recommends ample notice be provided to manufacturers and a pre-reassessment meeting to be available to manufacturers in order to clarify timelines, procedures and scope.
4.	Please feel free to comment on any other issues related to the proposed changes.
	Feedback CADTH should take into consideration the number of policy changes currently occurring in the Canadian environment. There needs to be caution around increasing uncertainty for manufacturers and thus de-incentivizing innovation medicine launches in Canada.