Canada's Drug Agency
L'Agence des médicaments du Canada

Procedures for Reimbursement Reviews

February 2025

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Abbreviations

ATC	Anatomic and Therapeutic Classification
BIA	budget impact analysis
CAPCA	Canadian Association of Provincial Cancer Agencies
CDA-AMC	Canada's Drug Agency
CDEC	Canadian Drug Expert Committee
CMA	cost-minimization analysis
CPEC	Canadian Plasma Protein Product Expert Committee
CUA	cost-utility analysis
DIN	Drug Identification Number
FMEC	Formulary Management Expert Committee
FWG	Formulary Working Group
HTA	health technology assessment
IAP	implementation advice panel
INESSS	Institut national d'excellence en santé et en services sociaux
MAIC	matching-adjusted indirect comparison
NOC	Notice of Compliance
NOC/c	Notice of Compliance with Conditions
NOD	Notice of Deficiency
NON	Notice of Non-Compliance
PACES	pharmaceuticals with anticipated comparable efficacy and safety
PAG	Provincial Advisory Group
pCODR	pan-Canadian Oncology Drug Review
pCPA	pan-Canadian Pharmaceutical Alliance
pERC	pCODR Expert Review Committee
PFA	provisional funding algorithm

PPRP	Plasma Protein and Related Product
PTBLC	Provincial and Territorial Blood Liaison Committee
PWLE	person with lived experience
RCT	randomized controlled trial
RFA	request for advice
RWE	real-world evidence

1. Introduction

1.1. Purpose of This Document

This document outlines the procedures for Canada's Drug Agency – L'Agence des médicaments du Canada (CDA-AMC) reimbursement review processes.

CDA-AMC may amend the *Procedures for Reimbursement Reviews,* and all matters related to its drug review processes. CDA-AMC may request feedback for procedural changes and the drug programs may also be consulted, as required. Amendments to, and clarifications of, the *Procedures for Reimbursement Reviews* and all related documents may be effected by means of directives (called Pharmaceutical Reviews Update) issued on an as-needed basis between revisions of these procedures. As such, this document must be read in conjunction with any relevant issues of the *Pharmaceutical Reviews Update*.

The procedures for our reimbursement review processes are summarized in the following sections:

- **Sponsored reimbursement reviews:** procedures for reimbursement review applications filed by pharmaceutical industry sponsors and provincially recognized tumour groups
- **Drug program-initiated reimbursement reviews:** procedures for requests filed by the participating drug programs for nonsponsored reimbursement reviews and requests for advice
- **Multiple drug reviews:** procedures for reviews involving multiple drugs, referred to as therapeutic reviews and streamlined drug class reviews
- **Implementation advice:** describes the procedures for the establishment of provisional funding algorithms for oncology drugs and provides supplemental implementation advice to the participating drug programs

1.2. Overview of Reimbursement Review Process

1.2.1. Drug Review Process

The objectives of the reimbursement review processes are to reduce duplication across jurisdictions and maximize the use of limited resources. CDA-AMC undertakes reviews of drugs and issues reimbursement recommendations and/or review reports to all federal, provincial, and territorial drug programs and cancer agencies that participate in the CDA-AMC review processes and Canadian Blood Services (together hereafter referred to as "drug programs"). It is important to note that reimbursement recommendations are nonbinding to the drug programs. Each drug program makes its own reimbursement decisions based on the CDA-AMC recommendation, in addition to other factors, including the plan's mandate, jurisdictional priorities, and financial resources.

1.2.2. Expert Committees

Reimbursement recommendations are provided by appointed, national, expert review committees. Each committee is composed of individuals with expertise in drug therapy, drug evaluation, and drug utilization, as well as public members who bring a lay perspective. The current committee members and terms of reference are listed on the website.

CDA-AMC currently has the following drug expert committees that provide drug-related recommendations and advice to the drug programs:

- The Canadian Drug Expert Committee (CDEC) is used for drugs that are non-oncology drugs reviewed through the reimbursement review process.
- The Canadian Plasma Protein Product Expert Committee (CPEC) is a subcommittee of CDEC that is used for products that are reviewed through the interim PPRP process.
- The pan-Canadian Oncology Drug Review Expert committee (pERC) is used for oncology drugs that are reviewed through the reimbursement review process.
- The Formulary Management Expert Committee (FMEC) is used for non-sponsored single drug reviews, streamlined drug class reviews, and therapeutic reviews as requested by federal, provincial, and territorial drug plans and cancer agencies.

All expert committee members must comply with the Conflict-of-Interest Policy and the Code of Conduct Agreement.

1.2.3. Advisory Committees

CDA-AMC also has several jurisdictional advisory committees and working groups that provide advice on drug policy issues. This includes the Pharmaceutical Advisory Committee, which advises CDA-AMC on strategic issues, as well as working groups that provide advice on operational issues. The primary working groups for advising on reimbursement reviews are the Provincial Advisory Group (PAG) for oncology drugs and the Formulary Working Group (FWG) for non-oncology drugs.

1.3. Communications for Reimbursement Reviews

1.3.1. Inquiries

Interested parties are asked to use the contact us form for inquiries related to the CDA-AMC reimbursement review processes. Inquiries should not be addressed directly to the program director or other CDA-AMC staff as this can disrupt the routine tracking and triaging of inquiries (and these types of disruptions can result in a lengthier time for obtaining a response). Consultants working on behalf of a sponsor are required to copy an official contact for the sponsor on all email correspondence with CDA-AMC. The agency will not respond to any email correspondence from a consultant if an official contact for the sponsor has not been copied.

- General inquiries regarding procedures and processes**:** contact us form
- Inquiries regarding an active review: formulary-support@cda-amc.ca
- Inquiries regarding SharePoint access: support@cda-amc.ca
- Inquiries regarding application fee: accountsreceivable@cda-amc.ca

1.3.2. Communications

All communications for drug review programs are issued in a single email newsletter once per week (typically on Thursday). The newsletter includes the following announcements and opportunities:

- calls for patient and clinician group input
- opportunities for feedback on draft recommendations and draft provisional algorithms
- notice of final recommendation
- notice of final provisional funding algorithm
- procedural updates and clarifications
- consultation opportunities
- other news regarding drug review programs.

1.4. Confidentiality and Document Management

Confidentiality guidelines have been developed to protect confidential information obtained through reimbursement review processes (Appendix 1). These confidentiality guidelines ensure that appropriate steps and procedures are in place to protect confidential information, and that this information will be handled in a consistent manner. CDA-AMC will comply with these confidentiality guidelines when handling information as part of the reimbursement review processes. A sponsor will be deemed to have consented to the confidentiality guidelines when it files an application, or when it supplies other information to CDA-AMC. A sponsor will maintain the confidentiality of documents shared with it by CDA-AMC. The confidentiality guidelines will constitute an agreement between CDA-AMC and the sponsor.

The CDA-AMC reimbursement review processes are complete when all relevant CDA-AMC documents have been posted on the CDA-AMC website (e.g., recommendation, review report[s], and patient and clinician group input) or the application has been withdrawn. CDA-AMC then undertakes the steps detailed in the confidentiality guidelines regarding the retrieval, disposal, and archiving of files associated with the review.

Sponsored Reimbursement Review

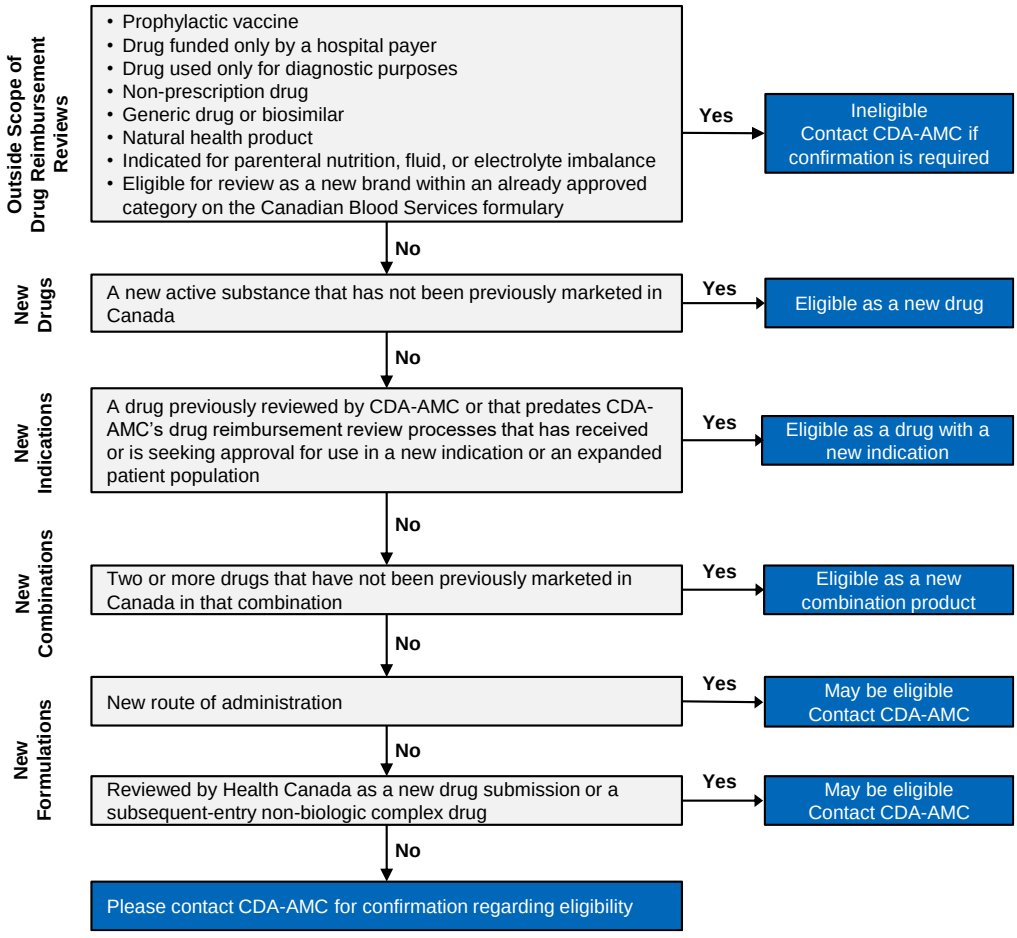
2. Eligibility for Sponsored Reviews

2.1. Submission Eligibility

2.1.1. Overview

This section provides guidance regarding eligibility for most submissions. In some situations, CDA-AMC may consult with the drug programs to confirm the eligibility of a drug and decide on a case-by-case basis. A sponsor or the drug programs may file an application for an eligible drug that has received or has a pending Notice of Compliance (NOC) or Notice of Compliance with conditions (NOC/c) for the indication(s) to be reviewed. In selected instances, CDA-AMC may undertake the review of a drug for an unapproved indication in accordance with the criteria specified in section 2.5.3.

Figure 1: Drugs Eligible for the Reimbursement Review Processes



2.1.2. Eligibility Criteria

2.1.2.1. New Drugs

A new drug, for reimbursement review submission purposes, typically includes one of the following:

- a new active substance that has not been previously marketed in Canada, regardless of when the NOC or NOC/c was issued
- a drug consisting of a single active substance previously reviewed through one of the reimbursement review processes only as an active substance in a combination product
- a new salt of a marketed product
- a drug for which eligibility for review has been confirmed in consultation with the drug programs on a case-by-case basis.

2.1.2.2. New Indications

A drug with a new indication is:

- a drug previously reviewed through one of the reimbursement review processes that has received an NOC or NOC/c for a new indication
- an active substance marketed before the establishment of CDA-AMC's reimbursement review processes that has received an NOC or NOC/c for a new indication
- a drug previously reviewed through one of the reimbursement review processes that is approved for use in a new age range for the patient population.

2.1.2.3. New Combination Products

A new combination product consists of 2 or more drugs that have not been previously marketed in Canada in that combination. One or more of the components may be a non-prescription drug, but at least one component must be a prescription drug.

2.1.2.4. New Formulations of Existing Drugs

A new drug for the purposes of a reimbursement review submission does not include the following variations of existing non-parenteral products containing the same active substance(s) as one or more drugs that have been previously reviewed through one of the reimbursement review processes and/or are currently being funded by the drug programs for the same indication (note: these are considered line extensions):

- a new non-parenteral dosage form with the same route of administration, if the new dosage form approval is not accompanied by a change to the indicated population age range (e.g., if a drug in tablet form becomes available in capsule or oral solution dosage form)

- a new strength of the same dosage form (e.g., if a 200 mg tablet becomes available in addition to an already-marketed 100 mg tablet, and the new strength approval is not accompanied by a change to the indicated population age range, a submission for the 200 mg tablet is not required).

New parenteral products or formulations (e.g., IV, intramuscular, subcutaneous dosage forms) are not considered line extensions of one another, as they have different routes of administration and, as a result, there may be potential differences in pharmacokinetics and pharmacodynamics, as well as differences in cost. Sponsors should submit a completed eligibility request form to CDA-AMC for guidance on whether a submission is required for a new parenteral formulation.

2.1.2.5. Plasma Protein and Related Products

Submissions for new categories and/or for new products that are determined to be in some way innovative to the Canadian Blood Services formulary will be assessed using the Canadian Blood Services Plasma Protein and Related Product (PPRP) selection eligibility criteria, subject to approval by the provincial and territorial governments (excluding Quebec) on the Canadian Blood Services formulary. The eligibility criteria are that the product:

- is a biological drug manufactured from human plasma or a biological drug whose active ingredient(s) are functional equivalents of the foregoing, used in the practice of Transfusion Medicine; AND
- is not carried in the health system already.

The review will be initiated after confirmation by the Provincial and Territorial Blood Liaison Committee (PTBLC) on whether the product meets the eligibility requirements for consideration as a new category and/or a new product that is determined to be in some way innovative on the Canadian Blood Services formulary.

Canadian Blood Services will confirm with the manufacturer if the product will also be reviewed through an RFP process for PPRPs in an approved category of products.

Manufacturers with questions regarding whether a product is eligible for review through the interim process are asked to complete an eligibility request form and submit it to CDA-AMC. The information will be forwarded to Canadian Blood Services for discussion with the PTBLC. Eligibility should be determined before requesting a presubmission meeting or providing advance notification. If it has been determined that the product does not meet the eligibility criteria as a PPRP, the sponsor can consider filing a submission through the reimbursement review process for a recommendation to inform reimbursement by the public drug programs.

2.1.2.6. Subsequent-Entry Products for Non-Biological Complex Drugs

A subsequent-entry non-biological complex drug is a medicinal product that demonstrates a high degree of similarity to an already authorized product (i.e., a reference product that has been approved for use in

Canada). Due to the complex nature of the product, demonstrating bioequivalence may not be possible. Submissions for subsequent-entry non-biological complex drugs will typically undergo a tailored review. All sponsors should contact CDA-AMC before filing a submission for a subsequent-entry non-biological complex drug.

2.1.2.7. Eligible Drugs That Have Become Genericized

As stated in section 2.1, generic drugs are not typically reviewed through the reimbursement review processes. This is usually because the branded reference product has previously been reviewed. In the event a submission was not filed for a branded drug before the drug became genericized, the drug programs will be consulted to determine whether either or both manufacturers of the generic or branded product should file a reimbursement review submission. Given that the context and product characteristics for these situations are likely to be unique, guidance will be provided on a case-by-case basis as to whether a submission is required. Based on the input from the drug programs, manufacturers of branded or generic products that are eligible for review through the reimbursement review process (e.g., a new drug, a drug with a new indication, or a new combination product) may be advised that submission is not required, and that the drug programs should be contacted.

Circumstances that would likely not require a submission to be filed may include, but are not limited to, the following:

- One or more generic versions of the drug are approved by Health Canada.
- One or more generic versions of the drug are undergoing review by Health Canada.
- The drug programs have indicated they are planning to review the generic drug(s) through their standard processes for reviewing generic drugs.
- Similar products are currently listed by the drug programs (e.g., different salts of the active substance).

A submission may be required for a generic product under the following conditions:

- Similar products are not currently listed by the drug programs (e.g., different salts of the active substance).
- The manufacturer of the branded product has confirmed that it does not intend to file the product for a reimbursement review and does not intend to seek public reimbursement.
- The generic product was reviewed by Health Canada as a new drug submission or supplemental new drug submission.

Although a manufacturer may be advised that a submission is not required, it does not preclude the manufacturer from electing to file a submission provided the product meets the eligibility criteria for a new drug, a drug with a new indication, or a new combination product. Manufacturers with questions regarding the reimbursement review processes may contact CDA-AMC any time.

2.1.2.8. Biosimilars

As stated in section 2.1, biosimilars are not typically reviewed through the reimbursement review processes. Applications are only required if the biosimilar meets other eligibility criteria (e.g., a new indication that is not approved for the reference product or a new formulation that is eligible for review). Each of those scenarios is approached on a case-by-case basis and a decision is made in consultation with the participating drug programs. Sponsors that have questions regarding whether or not a biosimilar is eligible for review must submit are asked to complete an eligibility inquiry form and submit it to CDA-AMC.

2.1.3. Eligibility Assessment

Sponsors that have questions regarding whether a drug is eligible for review are asked to complete an eligibility inquiry form and submit it to CDA-AMC as soon as possible. Eligibility should be determined prior to requesting a presubmission meeting or providing advanced notification.

2.2. Resubmission Eligibility

2.2.1. Overview

A resubmission is a review of any drug that has previously been reviewed through a reimbursement review process and for which a final recommendation has been issued. A resubmission is conducted when new evidence is available for a drug that has previously been reviewed for the indication of interest and for which a final recommendation has been issued. Resubmissions are typically limited to drugs that were not recommended for reimbursement by our expert committee and are not currently reimbursed by the drug programs for the indication of interest. The output of the review of a resubmission will be an updated recommendation document that will be supersede the document for the initial submission and any other prior resubmissions for the drug under review.

Eligibility must be confirmed prior to filing the resubmission by sending a completed eligibility form to CDA-AMC. The form will be reviewed, and confirmation will be provided to the sponsor, typically within 10 business days of receiving the form.

2.2.2. Eligibility Criteria

Table 1 summarizes the grounds for filing a resubmission and required information for the resubmission to be accepted for review.

Table 1: Resubmission Eligibility and Screening Criteria

Resubmission Grounds	Information Required
New clinical information in support of improved efficacy or safety (i.e., new clinical data that has not been previously submitted to CDA-AMC).	1 or more **new** clinical studies that address specific issues identified by the expert committee in the final recommendation
Request for reimbursement in a subpopulation.	Data for a subpopulation that was not previously the focus of the CDA-AMC with a revised reimbursement request focusing only on that subpopulation of patients. In these cases, the clinical information (e.g., subgroup analyses) may have been previously submitted but was not the focus of the evaluation by CDA-AMC or specifically reflected in the calls for input and feedback.[a]
New cost information that significantly affects the cost-effectiveness of the drug.	New pharmacoeconomic evaluation addressing the limitations that were identified by CDA-AMC for the previously submitted economic model.

[a] Do not reimbursement recommendations would typically describe committee deliberations on potentially relevant subpopulations, but there may be instances where that information was not reported in detail within the recommendation document. In these cases, CDA-AMC will review the previous deliberations in detail and may inform the sponsor that the issue has already been discussed by the committee and the proposed resubmission will not be accepted for review.

2.2.3. Eligibility Assessment

Resubmission eligibility must be determined prior to requesting a presubmission meeting or providing advanced notification to CDA-AMC. Prior to filing a resubmission, sponsors are required to have its eligibility assessed by CDA-AMC. Sponsors must provide the following information to CDA-AMC (using the Pharmaceutical Reviews SharePoint site) for evaluation:

- a completed eligibility form
- copies of the new clinical study(ies) or relevant subpopulation data.

The information provided by the sponsor will be screened by CDA-AMC to determine if is meets the eligibility requirements outlined in Table 1. As shown in Figure 2, members of the expert committee and/or clinical experts may be consulted to determine if the new information filed by the sponsor meets the eligibility criteria. However, the final decision regarding whether a resubmission or reassessment will be eligible for review will be determined by CDA-AMC. The assessment of eligibility will typically be completed within 10 business days. Sponsors will be notified if additional time is required to complete the assessment.

The sponsor will be apprised in writing regarding whether the proposed resubmission or reassessment meets the eligibility criteria. When a sponsor has been informed that the eligibility criteria have not been met, the sponsor may file one written request for the decision to be reconsidered. The request must

clearly outline why the sponsor disagrees with the decision. Sponsors have 10 business days to file a request after receiving notification regarding the eligibility of their proposed resubmission or reassessment. Sponsors will only be entitled to have the eligibility decision reconsidered once.

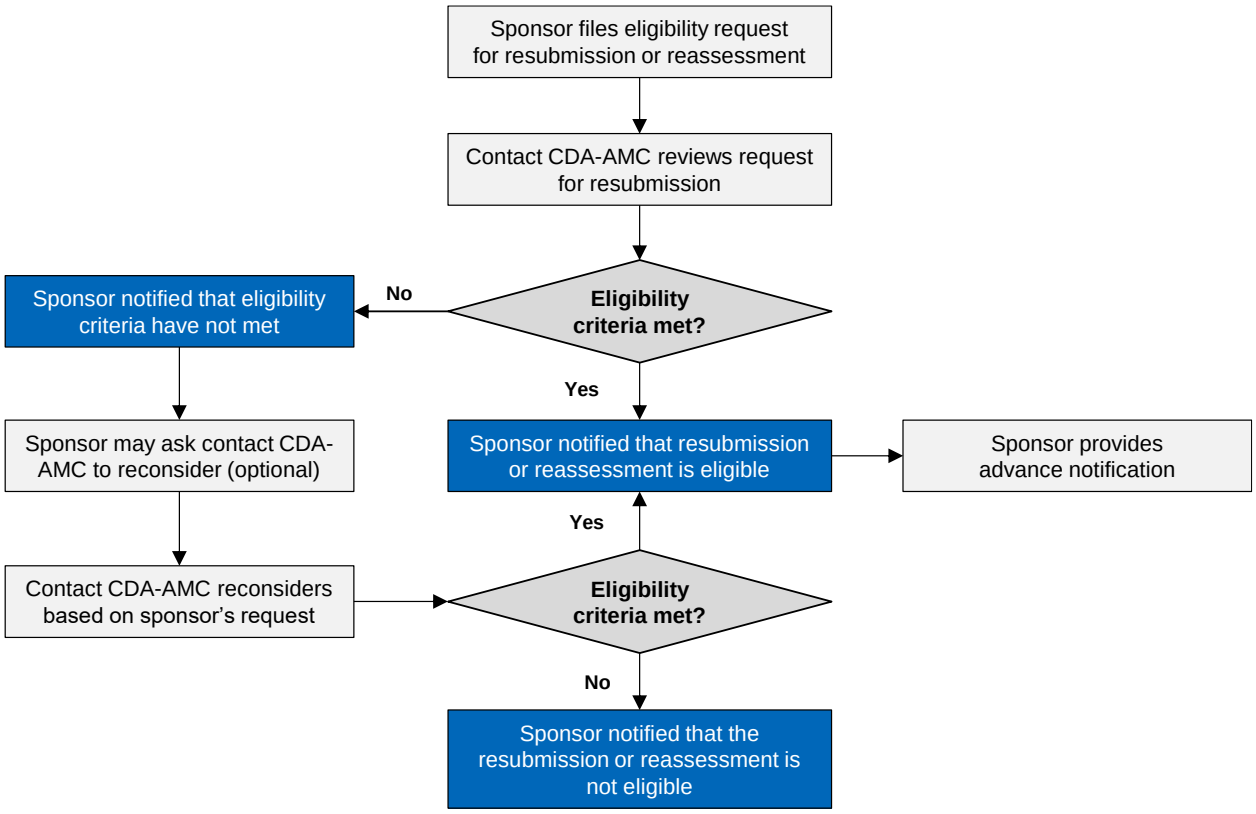
The request will be examined to determine whether the issue(s) raised change the conclusions regarding the eligibility of the resubmission or reassessment. Members of the expert committee and/or clinical experts (as required) may be consulted. The final decision regarding whether a resubmission or reassessment is eligible for review will be determined by CDA-AMC. The reconsideration will typically be completed within 10 business days, and sponsors will be notified if additional time is required to complete the assessment. The sponsor will be apprised in writing of the final decision regarding eligibility of the resubmission. The results of the resubmission or reassessment eligibility assessment may be posted on the website.

Documents associated with the resubmission or reassessment will be retained and dispose of in accordance with the confidentiality guidelines (Appendix 1). All completed eligibility assessments may be shared by CDA-AMC with the federal, provincial, territorial governments (including their agencies and departments) and the pan-Canadian Pharmaceutical Alliance (pCPA) office.

After receiving confirmation that the proposed application is eligible for review through a reimbursement review process, sponsors are required to provide advance notification in accordance with section 4.2.

To ensure fair access to the reimbursement review processes for new drug submissions, the number of resubmissions that can be made and/or initiated within a period may be limited. This decision will be made based on the availability of resources and will be communicated via a Pharmaceutical Reviews Update.

Figure 2: Assessing the Eligibility of Resubmissions or Reassessments



2.3. Reassessment Eligibility

2.3.1. Overview

Any drug that is currently reimbursed in the Canadian public health care system could be eligible for a reassessment. The sponsored reassessment process may be initiated in the following circumstances:

- Sponsor is proactively seeking revisions to any of the conditions associated with a previous reimbursement recommendation.
- Sponsor is filing the reassessment as mandated by a previous time-limited reimbursement recommendation.

2.3.2. Eligibility Criteria

To be eligible for a reassessment the sponsor must typically submit 1 or more new clinical studies that supports the sponsor's request for revised reimbursement criteria for the drug or be providing the reassessment to address the conditions in a time-limited reimbursement recommendation.

2.3.3. Eligibility Assessment

Similar to the resubmission process, sponsors that wish to proactively have a drug considered through the standard reassessment process will be required to submit (to the Pharmaceutical Reviews SharePoint site) an eligibility inquiry form and copies of one or more new studies that support the requested revisions to the reimbursement criteria for the drug. The information provided by the sponsor will be assessed using the same approach described for resubmissions in section 2.2.3. After receiving confirmation that the proposed reassessment is eligible for review, sponsors would be required to provide advance notification for the pending reassessment in accordance with procedures specified in section 4.2.

To ensure fair access to the reimbursement review processes for new drug submissions, the number of reassessments that can be made and/or initiated within a period may be limited. This decision will be made based on the availability of resources and will be communicated via a Pharmaceutical Reviews Update.

2.4. Time-Limited Recommendation Eligibility

2.4.1. Overview

A time-limited recommendation is a recommendation to publicly fund a drug or drug regimen for a certain period based on the condition that the sponsor will conduct 1 or more clinical studies that address the uncertainty, and that CDA-AMC will conduct a reassessment of the additional evidence. The future reassessment by CDA-AMC will lead to a final reimbursement recommendation.

2.4.2. Eligible Criteria

Drugs eligible for consideration for a time-limited recommendation are those with all the following characteristics:

1. **Regulatory review status**: The drug has been or is undergoing review through Health Canada's advance consideration process under the Notice of Compliance with Conditions (NOC/c) policy or the approval is accompanied by terms and conditions (CDA-AMC will continue to monitor Health Canada's initiatives on Regulatory innovation for health products: Agile licensing for drugs and would amend the process align with any confirmed revisions to the NOC/c process in Canada).
2. **Evidence-generation plans:** A phase III clinical trial is being planned and/or conducted in the same patient population at the time of the submission to CDA-AMC and the study completion date will not exceed 3 years from the target expert committee meeting date.
    - The phase III study must be conducted in the same patient population as the indication under review (e.g., same line of therapy) and using the same intervention being reviewed by CDA-AMC (e.g., the same dosage regimen specified in the product monograph). The final decision

regarding the relevance of the population and the intervention will be determined by CDA-AMC.

- Study completion refers to the target date that will be publicly communicated through clinicaltrials.gov (i.e., the date the final study participant will be examined or received an intervention for the purpose of the final collection of data for the primary and secondary outcome measures and adverse events).
- In the event the sponsor anticipates a scenario where interim study results will be available within the 3-year study period and would expect those data to inform the removal of conditions associated with the regulatory approval, CDA-AMC will discuss eligibility with the sponsor on a case-by-case basis.

3. **Reassessment commitment:** The sponsor has expressed a commitment to file a reassessment application with CDA-AMC in accordance with the time frames specified in the procedures for time-limited recommendations (i.e., within 270 calendar days after the completion date of the phase III trial).
   - In a situation where a drug meets the eligibility criteria based on the regulatory review status and the evidence generation plans, but the sponsor will not commit to filing a reassessment application with CDA-AMC in accordance with the time frames specified in the procedures for time-limited recommendations, the expert committee will be informed of the sponsor's decision and that a time-limited recommendation will not be an option for the drug under review. In such cases, the drug will be reviewed in accordance with CDA-AMC procedures for drugs that ineligible for a time-limited recommendation.
   - Sponsors must declare their willingness to participate in the time-limited recommendation from the outset of the process (i.e., when the application is initially filed). Sponsors who do not consent from the outset of the process will not be permitted to request consideration for a time-limited recommendation as part of a request for reconsideration following issuance of a draft recommendation.
   - Any sponsors who initially decline to commit to the time-limited recommendation process at the time the application is filed but subsequently wish to participate will be required to withdraw and refile the application.
4. **Evidentiary gaps:** The evidence-generation plans described in Health Canada's qualifying notice are expected to address the gaps in the evidence identified by the expert committee.

Any drugs that do not meet all the eligibility criteria will not be considered for a time-limited recommendation. In addition, products that are reviewed through the Interim Plasma Protein and Related Products Process (i.e., those targeted for consideration by Canadian Blood Services) will not be eligible for time-limited recommendations at this time.

2.4.3. Eligibility Assessment

Sponsors with products that may be eligible for consideration through the time-limited recommendation process must submit an eligibility inquiry form to the Pharmaceutical Reviews SharePoint site. With the inquiry form, the sponsor will be required to address the eligibility criteria regarding the regulatory review status, the evidence-generation plans, and their ability and willingness to file a reassessment application with CDA-AMC in accordance with the time frames specified section 8.5.5.

CDA-AMC will document the sponsor's responses to the eligibility questions and conduct an initial assessment to determine if the eligibility criteria for a time-limited recommendation have been met. CDA-AMC appreciates that complete details regarding the evidence generation plans may not be available in the presubmission phase. In those cases, preliminary plans should still be communicated. It is important to note that the final decision on whether a time-limited recommendation will be issued will be made by the expert committee after it concludes that there is sufficient evidence to issue an initial recommendation in favour of reimbursement based on the preliminary data that is available at the time of the review.

Sponsors will be notified regarding the decision on eligibility. For drugs that are eligible for consideration through the time-limited recommendation process, the project webpage will be updated to state that the following: Eligible for consideration as a time-limited recommendation.

Drugs that are not eligible to be considered for a time-limited recommendation would be reviewed in accordance with the standard CDA-AMC procedures and recommendation framework. Any sponsors who disagree with the eligibility decision should contact the project coordinator with complete details regarding why the sponsor believes the incorrect decision was made. CDA-AMC will work with the sponsor on a case-by-case to clarify or revise the eligible decision as required.

2.5. Market Authorization Status

Submissions can be filed prior to receiving market authorization from Health Canada (i.e., pre-NOC submissions) or after receiving market authorization from Health Canada (i.e., post-NOC submissions).

2.5.1. Pre-NOC Submissions

Any submission may be filed on a pre-NOC basis up to 180 calendar days in advance of the anticipated receipt of an NOC or NOC/c. If the 180th calendar day falls on a weekend or holiday, the next business day will be used. Pre-NOC submissions may only be filed by industry sponsors (refer to section 2.6.1).

This type of submission is accepted with the agreement that some submission requirements (e.g., product monograph) may not be finalized at the time of filing; however, they are to be provided as soon as they are finalized because the draft recommendation will not be released until all required information, including a copy of the NOC or NOC/c, has been received by CDA-AMC.

Sponsors must proactively notify CDA-AMC regarding important changes to the indication and/or dosing information during the review of pre-NOC submissions. Sponsors will receive a request from CDA-AMC 20 business days prior to the target date for the expert committee meeting to confirm the following:

- if there are any revisions to the anticipated date of approval by Health Canada;
- if the sponsor is anticipating or discussing revisions to the indication and/or dosing information regarding the drug under review.

Sponsors will be required to provide a written response within 3 business days of receiving the request.

2.5.2. Post-NOC Submissions

A submission may be filed on a post-NOC or NOC/c basis after the drug has been granted an NOC or NOC/c by Health Canada for the indication(s) to be reviewed through the reimbursement review process.

2.5.3. Submissions for Unapproved Indications

Submissions may be filed for oncology drugs for new indications that are not approved or are not undergoing review by Health Canada in the following instances:

- the drug is currently marketed in Canada
- the Drug Identification Number (DIN) holder confirms that a submission to Health Canada is not pending for the indication of interest
- the DIN holder confirms that a submission to Health Canada has not been made in the past for the indication of interest and received a Notice of Deficiency (NOD) or Notice of Non-Compliance (NON)
- there is sufficient clinical evidence for the new indication to support a submission
- the drug has the potential to address an unmet therapeutic need.

This information will be considered when determining whether a submission may be filed for an indication that is not approved or are not undergoing review by Health Canada and will waive the required documents that are related to regulatory review and approval for these submissions: Common Technical Document; Health Canada NOC or NOC/c; and table of Clarimails/Clarifaxes.

2.6. Sponsor Eligibility

2.6.1. Industry Sponsors

Pharmaceutical industry sponsors are typically the DIN holders for the drug being filed for review; however, it could be another manufacturer, supplier, distributor, or other entity that has been recruited by the DIN holder.

2.6.2. Tumour Groups and Drug Programs

The drug programs and provincially recognized clinician-based tumour groups may file applications through the reimbursement review processes. Tumour groups will need to work with one of their jurisdictional PAG members to bring forward their intention to make an application. PAG will assist in determining if the application would be of sufficient interest to warrant a review and recommendation or if it could be addressed within the individual jurisdictions.

Prior to accepting a new submission from a tumour group or the drug programs, CDA-AMC will confirm with the DIN holder that they are declining to file a submission (i.e., in accordance with section 2.7).

It is expected that tumour groups and drug programs will not have the same access to information as the manufacturer of the drug. Therefore, the following requirements will be waived if they are unavailable or not relevant: Common Technical Document; Clinical Study Reports; Health Canada NOC or NOC/c; Table of Clarimails/Clarifaxes. Sponsors from tumour groups and the drug programs will be required to include an economic evaluation in their application.

The DIN holder may be contacted on behalf of the tumour group and/or drug programs to determine if there is interest in providing relevant clinical and pharmacoeconomic data for the purpose of compiling the required documentation for the pending application.

In general, the review process will be the same as that used in the review of an application filed by an industry sponsor.

2.7. Declining to File a Submission

The following process will be applied in situations where a manufacturer does not proactively file a submission for an eligible product:

- Jurisdictions determine that they require a recommendation to inform their reimbursement decisions.
- A letter will be issued to the manufacturer on behalf of the Pharmaceutical Advisory Committee FWG or PAG informing it that the drug is eligible for review through the reimbursement review processes and that the drug programs would like a submission to be filed.
- The manufacturer will have 15 business days to respond to the letter indicating whether it is planning to file a submission for the drug, as well as its anticipated timelines for the submission.
- In the following scenarios a “Canada’s Drug Agency is unable to make a reimbursement recommendation as the manufacturer has not filed a submission” statement will be issued on the website:
    - a manufacturer indicates that it is not planning to file a submission at this time

- a manufacturer fails to respond to the FWG or PAG chair within the requested 30 business day period
- a manufacturer indicated that a submission would be filed but did not provide advance notification with the anticipated filing date within 12 months of receiving the request from the FWG or PAG chair.

- These statements will be issued on the basis that a submission was not filed by the manufacturer and will not be discussed by the expert committees.
- The procedure will only apply to submissions and not to resubmissions.
- If a statement has been issued on the basis that a submission was not filed, the manufacturer may file a submission at any point in the future in accordance with the reimbursement review procedures. This would result in a reimbursement recommendation being issued for the drug and the previous statement being removed from the website.
- The participating jurisdictions can continue to file drug program–initiated submissions provided the requirements can been addressed (e.g., provision of an economic model and pharmacoeconomic evaluation).

3. Application Types

CDA-AMC aims to conduct its reviews in the most efficient manner and applies the following review types depending on the complexity of the reimbursement review: tailored, standard, and complex. The following section describes the eligibility criteria and key features of each application type. Key information about the review categories is summarized in Table 2. Details about the eligibility criteria for complex and tailored reviews are summarized in sections 3.2 and 3.3, respectively.

Please note that eligibility for review through the tailored and complex processes must be confirmed prior to filing the submission by uploading an eligibility inquiry form to the Pharmaceutical Review SharePoint site. The form will be reviewed, and the sponsor will typically be notified within 10 business days.

The output of the review of an initial submission will be a recommendation document advising the drug programs on whether the drug under review should be reimbursed and under what conditions reimbursement should be considered.

Table 2: Summary of Reimbursement Review Project Type

Criteria	Complex Review	Standard Review	PACES Tailored Review	Product Variation Tailored Review
Eligibility criteria				
Key eligibility criteria	Drugs with added complexity, as described in section 3.2	All files that are not eligible for tailored or complex reviews	Same indication and therapeutic class as ≥ 1 other drug previously	New combination products and new formulations (refer to section 3.3.2)

Criteria	Complex Review	Standard Review	PACES Tailored Review	Product Variation Tailored Review
			recommended (refer to section 3.3.1)	
Clinical information				
Pivotal trials and RCT evidence	Required	Required	Required	Required
Indirect comparison[c]	Accepted	Accepted	Accepted[d]	Not accepted
Long-term extension data	Accepted	Accepted	Not accepted	Not accepted
Studies addressing remaining gaps in evidence[e]	Accepted	Not accepted	Not accepted	Not accepted
Economic submission information				
Economic evaluation	CUA or CMA	CUA or CMA	CMA	Cost-comparison table[f]
Budget impact analysis	Required	Required	Required	Required
Recommendation				
Expert committee	CDEC or pERC	CDEC or pERC	Subcommittee	Subcommittee
Target timelines				
Timelines from acceptance to draft recommendation	≤ 180 calendar days	≤ 180 calendar days	100 to 120 calendar days	100 to 120 calendar days
Application Fee				
Fee schedule	Schedule E	Schedule A	Schedule B	Schedule C

CDEC = Canadian Drug Expert Committee; CMA = cost-minimization analysis; CUA = cost-utility analysis; PACES = pharmaceuticals with anticipated comparable efficacy and safety; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; RCT = randomized controlled trial

[a] Recommendations for non-oncology and oncology drugs are issued by CDEC and pERC respectively (or a subcommittee of those members).

[b] The performance metric will remain ≤ 180 calendar days from acceptance for review to issuance of the draft recommendation.

[c] Evidence of comparative effectiveness and/or harms using methodologically appropriate indirect comparison methods.

[d] Refer to section 3.3.1 for details on acceptable forms of indirect comparative evidence for PACES reviews.

[e] Additional evidence submitted to address gaps in the pivotal clinical trial, RCT, and direct or indirect comparative effectiveness and/or safety evidence (e.g., single-arm, open-label [interventional] trials, RWE and other observational studies, and/or long-tern extension [clinical] studies).

[f] The required cost-comparison table is embedded in the tailored review submission template for all product variation tailored review applications.

3.1. Standard Review

The standard review is the most common application type and will apply to all applications that do not meet the criteria for review through the tailored review or complex review processes. It is important to note the sponsor is responsible for contacting CDA-AMC concerning eligibility for review through the standard and complex review processes before the application is filed (i.e., if the sponsor files an application through the standard review process, CDA-AMC will not be responsible for evaluating eligibility for review through the tailored or complex review processes unless specifically requested by the sponsor).

3.2. Complex Review

A complex review includes process enhancements that are applied in a manner that is targeted to the specific challenges posed by the drug under review.

3.2.1. Scenario 1: First Drug Approved in the Therapeutic Area

3.2.1.1. Eligibility Criteria

The drug under review must meet all the following criteria:

- The sponsor is claiming added clinical benefit compared with the most appropriate comparator(s) or best supportive care.
- It is the first drug approved by Health Canada for use in the therapeutic area.
- There are no unapproved comparator drugs with well-established reimbursement criteria in the therapeutic area.

For therapeutic areas where there may be multiple lines of therapy administered for the target patient population (e.g., lines of therapy for an oncology indication), the criterion for a complex review would be met for the first drug specifically indicated for the target type (of cancer), but not for subsequent submissions that may follow for different lines of therapy (for that cancer type). Similarly, a drug with a novel biomarker could be classified as a complex review for the first application, but subsequent applications for different cancer types would be reviewed through the standard review process.

3.2.1.2. Potential Challenges With These Applications

Applications meeting scenario 1 complex review criteria may offer the following challenges:

- Novel reimbursement conditions would be required (i.e., new initiation, renewal, discontinuation, and prescribing criteria). These must be developed in consultation with multiple clinical specialists to avoid implementation challenges.

- Existing therapies may be used in an off-label manner and lack robust clinical data to inform estimates of comparative effectiveness (e.g., older drugs that are used as the standard therapies for the target patient population).
- Some novel drugs may pose ethical challenges for the expert committee and/or decision-makers. While many therapies and their contexts raise ethical considerations, some therapies raise specific and unique considerations and warrant a more in-depth Ethics Review.

3.2.1.3. Process Enhancements for These Applications

The following process enhancements will typically be applied for applications meeting scenario 1 complex review criteria:

- More clinical experts will be consulted throughout the review.
- A person with lived experience with the condition under review will be engaged to participate in the expert committee meeting.
- A societal perspective base case, alongside the health care payer perspective base case, may be filed for the economic evaluation.
- A separate Ethics Review report may be prepared based on several sources, including a dedicated review of the ethics literature relevant to the therapy under review and target population. Additional presentations from the ethicist members on the expert committees would also be warranted during the expert committee deliberations.
- Additional studies addressing important gaps in evidence may be included in the CDA-AMC report and reflected in the expert committee's deliberations.

3.2.2. Scenario 2: Drugs With the Potential to Alter Existing Treatment Paradigms

3.2.2.1. Eligibility Criteria

The drug under review must meet all the following criteria:

- The sponsor is claiming added clinical benefit compared with the most appropriate comparator(s).
- It is not the first drug approved in the therapeutic area but has the potential to alter the treatment paradigm based on superior efficacy and/or safety.
- It has been granted priority review by Health Canada (e.g., an application for a drug indicated for the treatment of a serious, life-threatening, or severely debilitating disease or condition for which there is substantial evidence of clinical effectiveness, demonstrating that the drug provides a significant increase in efficacy and/or significant decrease in risk, such that the overall risk-benefit profile is improved over existing therapies, preventives, or diagnostic agents for a disease or condition that is not adequately managed by a drug marketed in Canada) or has been accepted for review through the Health Canada's advance consideration process under the NOC/c policy.

3.2.2.2. Potential Challenges With These Applications

Applications meeting scenario 2 complex review criteria may offer the following challenges:

- Novel reimbursement conditions may be required (i.e., new initiation, renewal, discontinuation, and prescribing criteria). These must be developed in consultation with multiple clinical specialists to avoid implementation challenges.
- Claims of added clinical benefit may require additional consultation with clinical specialists to evaluate the anticipated clinical relevance in routine practice, as the incremental benefit would directly influence the economic evaluation and pricing condition issued by the expert committee (e.g., price negotiation would likely involve the conclusions of the cost-effectiveness evaluation as opposed to the existing price of relevant comparator[s]).

3.2.2.3. Process Enhancements for These Applications

The following process enhancements will typically be applied for applications meeting scenario 2 complex review criteria:

- More clinical experts may be consulted throughout the review.
- A person with lived experience with the condition under review will be engaged to participate in the expert committee meeting.
- Additional consultation with methodologists may be required to appraise the evidence.
- Additional studies addressing important gaps in evidence may be included in the CDA-AMC report and reflected in the committee's deliberations.

3.2.3. Scenario 3: Primary End Point Is a Novel Surrogate Outcome

3.2.3.1. Eligibility Criteria

The sponsor's clinical data includes the evaluation of novel surrogate end points as the primary outcome(s) of their clinical trials (e.g., end points not previously reviewed by CDA-AMC).

3.2.3.2. Potential Challenges With These Applications

Novel surrogate end points will require additional validation by CDA-AMC to ensure the interpretation and appraisal of clinical evidence is appropriate.

3.2.3.3. Process Enhancements for These Applications

The following process enhancements will typically be applied for applications meeting scenario 3 complex review criteria:

- More clinical experts may be consulted throughout the review.
- Additional consultation with methodologists may be required to appraise the evidence.

- Additional studies addressing important gaps in evidence may be included in the CDA-AMC report and reflected in the committee's deliberations.

3.2.4. Scenario 4: Tumour-Agnostic or Histology-Independent Therapies

3.2.4.1. Eligibility Criteria

Any application for a tumour-agnostic or histology-independent indication will be considered a complex review by CDA-AMC.

3.2.4.2. Potential Challenges With These Applications

These applications require consultation with specialists representing multiple different areas of clinical practice. In addition, sponsors will typically submit multiple indirect comparisons and economic evaluations that have increased complexity relative to what is acceptable for an application reviewed through the standard process.

3.2.4.3. Process Enhancements for These Applications

The following process enhancements will typically be applied for applications meeting scenario 4 complex review criteria:

- More clinical experts may be consulted throughout the review.
- Additional consultation with methodologists may be required to appraise the evidence.
- Additional studies addressing important gaps in evidence may be included in the CDA-AMC report and reflected in the committee's deliberations.

3.2.5. Scenario 5: Additional Evidence With an Application Not Qualifying for Scenarios 1 to 4

3.2.5.1. Eligibility Criteria

The sponsor has additional evidence to address gaps in the pivotal clinical trial, RCT, and direct or indirect comparative effectiveness and/or safety evidence (e.g., real-world evidence in relevant patient populations that were not included in the clinical trials), but the application is not otherwise eligible for review through the complex process. This evidence may include:

- studies designed to demonstrate safety and effectiveness in relevant patient populations that were not included in the clinical trials
- studies designed to address outcomes that require longer-term follow-up and were not investigated in the clinical trials and/or extension studies
- studies that address uncertainty regarding the dosage of the drug under review that is used in actual clinical practice.

3.2.5.2. Potential Challenges With These Applications

Additional CDA-AMC resources are required to review the supplemental evidence included within the application.

3.2.5.3. Process Enhancements for These Applications

The additional studies would be included in the CDA-AMC report and reflected in the committee deliberations.

3.3. Tailored Review

A tailored review consists of an appraisal of the clinical evidence and pharmacoeconomic evaluation filed by the sponsor using a tailored review template. For applications that meet the eligibility criteria outlined in the sections that follow, it is important to note that it is the sponsor's decision to file an application through the tailored review process.

For tailored review applications, the recommendation would typically include a single pricing condition that the total cost of the drug under review should not exceed the total cost of the appropriate comparator(s). The appropriate comparator for the pricing condition would typically be the least costly comparator reimbursed for the condition of interest. It is important to note that the exclusion of a relevant comparator from the application by the sponsor does not mean that a comparator will not be considered appropriate for the purposes of a pricing condition.

3.3.1. PACES Tailored Review

3.3.1.1. Description

Tailored review submissions for pharmaceuticals with anticipated comparable efficacy and safety (PACES) will involve the sponsors submitting an abbreviated Summary of Clinical Evidence and Economic Evaluation template. This template includes the following sections:

- Key background information regarding the drug under review and the condition for which it is indicated.
- Results from a systematic literature review
- Results from indirect treatment comparisons.
- A summary of the key components of the economic evaluation.

Please note that, in addition to completing the economic summary in the tailored review template, the pharmacoeconomic submission requirements for cost-minimization analyses apply for PACES submissions (refer to section 6.6.2).

3.3.1.2. Eligibility Criteria

A PACES tailored review may be filed when an application meets all of the following criteria.

- **Sponsor's clinical claim:** The sponsor is not claiming added clinical benefit compared with appropriate comparators.
- **Indicated patient population:** The drug under review must have the same or a similar indication as at least 1 other drug previously reviewed by CDA-AMC and recommended for reimbursement.
- **Sponsor's requested reimbursement criteria:** The sponsor is requesting alignment with existing criteria that have been recommended by CDA-AMC and/or are currently used for the reimbursement of the most appropriate comparator(s).
- **Intervention:** The drug under review is within the same therapeutic class as at least 1 other drug previously reviewed by CDA-AMC and recommended for reimbursement.
- **Therapeutic regimens:** The new application and the previous application(s) for comparators must have evaluated the use of the drugs using the same regimen (e.g., as monotherapy or in combination with the same background therapies).
- **Comparators:** CDA-AMC has previously reviewed the most appropriate comparator(s) for the indication under review and issued recommendations in favour of reimbursement. The comparator will typically be a drug with the same indication, in the same therapeutic classification based on the 4th level of the Anatomic and Therapeutic Classification (ATC) System, and with the same mechanism of action.
- **Outcomes:** The end points evaluated by the sponsor align with those previously reviewed by CDA-AMC for applications in the same therapeutic area.
- **Clinical evidence:** The sponsor has evidence that the drug under review demonstrates similar clinical effects (i.e., has at least equivalent effectiveness and/or efficacy, and is equivalently or less harmful) compared to each of the most appropriate comparator(s) in one of the following formats:
    - direct comparative evidence from a randomized controlled trial (RCT)
    - Indirect comparative evidence that is based on aggregate clinical trial data (e.g., a mixed treatment comparison network meta-analysis).
    - Indirect comparative evidence that includes a single anchored matching-adjusted indirect comparison (MAIC).
    - Sponsors with any other forms of indirect evidence (e.g., unanchored MAIC) must file the application through the standard review process. Please note that other forms of indirect comparison may be more appropriate for the sponsor to provide evidence of the comparative clinical efficacy of the drug under review. The eligibility criteria for the PACES tailored review process should not be considered advice concerning the most appropriate methodology for indirect comparison and the choice of methodology rests solely with the sponsor. Prior to a

review being initiated, CDA-AMC will not conduct preliminary evaluations of the sponsor's indirect comparison to advise on methodology. The eligibility criterion will only be evaluated based on presence or absence of the information and will not be based on a detailed appraisal of the clinical evidence filed by the sponsor (i.e., that occurs during the review phase and not in the screening phase). Acceptance of an application for review through the tailored review process does not imply that CDA-AMC has concluded that the drug under review has demonstrated comparable clinical benefit to the appropriator comparators(s).

3.3.2. Product Variation Tailored Review

3.3.2.1. Description

CDA-AMC allows tailored review applications to be filed for selected new combination products and selected new formulations of existing drugs. These applications are referred to as product variation tailored reviews and consist of the CDA-AMC conducting an appraisal of the clinical evidence and pharmacoeconomic evaluation filed by the sponsor using the Product Variation Tailored Review template.

3.3.2.2. Eligibility Criteria for New Combination Products

A product variation tailored review may be filed when an application meets all of the following criteria.

- **Sponsor's clinical claim:** The sponsor is not claiming added clinical benefit compared with the most appropriate comparator(s).
- **Population:** The individual components of the drug are currently indicated for use in combination therapy with one another (i.e., the new combination product does not represent a new indication for the components).
- **Intervention:** The new combination product must not contain a new active substance. The individual components should be marketed in Canada in the same dosage strength as the new combination product.
- **Comparators:** The new combination product is intended to replace the separate use of the individual components.
- **Reimbursement status:** The individual components of the new combination product have been recommended by CDA-AMC and/or are reimbursed by the participating drug plans for use in the same combination.

3.3.2.3. Eligibility Criteria for New Formulation of an Existing Drug

- Product variation tailored reviews may be filed when an application meets all of the following criteria.
- **Sponsor's clinical claim:** The sponsor is not claiming added clinical benefit compared with the most appropriate comparator(s).

- **Population:** The indication(s) under review for the new formulation must be the same as the indication(s) previously reviewed and/or currently reimbursed by the participating drug programs for the existing formulations of the drug.
- **Intervention:** The new formulation must meet the eligibility criteria outlined in section 2.1.2.4 (e.g., new formulations of existing drugs that have a different route of administration than formulation[s] previously reviewed through the Reimbursement Review process).
- **Comparators:** The new formulation of the drug is intended to replace an alternative formulation of the same drug (e.g., the sponsor has a new subcutaneous formulation that would replace an existing IV formulation).

4. Presubmission Procedure

4.1. Confirming Application Eligibility and Review Type

Any sponsors with outstanding questions should submit an eligibility inquiry form using the Pharmaceutical Review SharePoint site prior to filing the application. CDA-AMC will review the information and provide guidance or recommend a presubmission meeting for further discussion. This includes all inquiries related to the following:

- General eligibility inquiries (i.e., for sponsors seeking guidance on whether a product is eligible for the Reimbursement Review process)
- Eligibility for the complex review process
- Eligibility for the tailored review process
- Eligibility for a time-limited reimbursement recommendation
- Eligibility for a resubmission or reassessment
- Requests for deviation from the pharmacoeconomic requirements
- Eligibility for the rolling submission pilot process
- Eligibility for a testing procedure assessment
- inquiries regarding application splitting and/or multiple application fees

4.2. Advance Notification Form

4.2.1. Filing the Advance Notification Form

Sponsors are required to provide a minimum of 30 business days advance notice for anticipated submissions and resubmissions. All sponsors are encouraged to provide as much notice as possible to facilitate resource planning and budgeting for the pharmaceutical review programs (≥ 120 calendar days is preferred). Sponsors who provided less than 30 business days' notice will be required to revise the anticipated filing date to meet the minimum requirement. To fulfill the advance notification requirement,

sponsors must complete the advance notification template in its entirety and upload to the Pharmaceutical Submissions SharePoint site in the "Advance Notification" folder. The 30–business day notification period will be counted from the date of receipt of the advance notification template to the targeted filing date for all anticipated applications.

Information provided as part of the advance notification process may be shared with the federal, provincial, and territorial governments, including their agencies and departments, as well as the pCPA office.

For resubmissions and reassessments, sponsors are required to receive eligibility confirmation from CDA-AMC before providing advance notification. The eligibility assessment and advance notification processes must occur sequentially to ensure that the patient and clinician group engagement process is only initiated for resubmissions and reassessments that are eligible for review by CDA-AMC.

Sponsors who provide notification more than 30 business days before the anticipated date of filing are required to confirm the anticipated filing date 30 business days in advance (Table 3).

Table 3: Advance Notification Process

Advance notification process	Days prior to anticipated filing date
Preferred advance notification	≥ 120 calendar days
Minimum mandatory advance notification	30 business days
Confirmation of anticipated filing date	30 business days[a]
Call for patient and clinician group input issued	29 business days

[a] Required only if more than 30 business days' advance notice was provided.

4.2.2. Revisions to the Anticipated Filing Date

A sponsor is required to advise CDA-AMC of any changes in the anticipated date of filing an application by uploading a revised template to the Pharmaceutical Submissions SharePoint site as soon as possible. For changes to an anticipated filing date made before posting the pending application on the website and issuing the call for input from patient groups and clinician groups, the timelines will be adjusted based on the new anticipated filing date. For changes to an anticipated filing date made after the pending application has been posted on the website, and the call for input from patient and clinician groups has been issued, the call for input will remain open for a total of 35 business days from the date the call was issued in the weekly email update. CDA-AMC strongly discourages sponsors from revising the anticipated filing date after the mandatory 30 business day confirmation has been provided. The confirmed anticipated filing date is the basis for resourcing the project and establishing review timelines. Applications received earlier than the confirmed anticipated filing date will be held and considered received only on the anticipated filing date.

Important note: CDA-AMC establishes the project teams and sets the target committee meeting agenda at the closing of a submission window (e.g., the range of dates during which an application may be filed to target a particular committee meeting).

- If a sponsor has provided advance notice and subsequently encounters a delay in their filing timelines, such that they are unable to file the application within the initially targeted submission window, they must provide CDA-AMC with a new target submission date before the closing of a submission window.
- If a sponsor fails to provide a target submission date by the closing of the submission window, the application will not be resourced, and the earliest filing date will automatically be moved to the next expert committee meeting.
- The earliest filing date will continue to be moved until the sponsor has confirmed the target submission date.

4.2.3. Posting Information About a Pending Application

Information regarding a pending application will be posted on the website at the time the call for patient and clinician group input is issued (i.e., 29 business days before the anticipated filing date).

4.3. Proposed Place in Therapy for Oncology Drugs

At the time of providing advance notification, all sponsors with pending applications for oncology drugs are required to provide a completed proposed place in therapy template. The proposed place in therapy template will provide the following information:

- the sponsor's proposed place in therapy for the drug under review, including a clearly stated rationale for the proposed place in therapy with supporting references (as required)
- an overview of the existing treatment algorithm for the indication of interest
- a proposed algorithm showing the place in therapy for the drug or regimen under review and the potential impact on the place in therapy of the currently reimbursed treatment options.

CDA-AMC will screen this template for completeness and will follow up with the sponsor if there is any information missing or anything that requires clarification.

During the review phase, the sponsor's proposed place in therapy for the drug under review will be considered, including discussion with clinical experts and critical appraisal of relevant supporting evidence. The drug programs will review the information contained in the proposed place in the therapy when considering the potential implementation issues associated with the drug under review. This may include a request to initiate implementation support activities to advise on the impact of reimbursing the drug under review on the existing funding algorithm within the indication.

4.4. Health Canada Information Sharing

4.4.1. Consenting to Information Sharing

As described in *Notice to industry: Aligned reviews between Health Canada and health technology assessment organizations*, an optional information-sharing process for submissions filed on a pre-NOC basis has been established to permit Health Canada and CDA-AMC to exchange information regarding the drug under review. Participation in this process could ensure that CDA-AMC has advance notice of any issues that have the potential to impact our review of the drug (e.g., changes to the indicated patient population), which could help avoid delays in the issuance of reimbursement recommendations.

Sponsors must indicate on the advance notification form (i.e., received ≥ 30 business days in advance of the submission filing date) whether they have consented or will be consenting to participate in the information-sharing process with Health Canada.

To promote alignment of regulatory and reimbursement reviews, sponsors should consent to information sharing at the time of, or prior to, submission filing with Health Canada. This may help to minimize the time between issuance of market authorization and the reimbursement recommendation. If the sponsor is unwilling to participate in the information-sharing process with Health Canada, CDA-AMC will continue to request information directly from the sponsor.

A secure portal will be used to exchange documents between Health Canada and CDA-AMC.

In the interest of transparency, CDA-AMC will indicate whether a sponsor has consented to participate in the information-sharing process (if applicable).

4.4.2. Invitations to Health Canada Presubmission and Pipeline Meetings

CDA-AMC welcomes opportunities to observe Health Canada presubmission meetings, pipeline meetings, or pre–clinical trial application consultation meetings. To streamline the process and reduce the administrative burden for sponsors, we ask that industry please note the following instructions:

4.4.2.1. Sending an Initial Request

Where to send the initial request: To ensure proper tracking and triage of the meeting request, please ensure that the request for attendance is sent only to CDA-AMC using the online inquiry form.

What information must be included: To ensure appropriate attendance at the meeting, please include the following information in the initial request:

- Meeting date and time
- Meeting location (i.e., confirmation that virtual attendance is acceptable)
- For presubmission meetings: Drug name and the proposed indication

- For pipeline meetings: please note if the presentations will focus on a particular therapeutic area (oncology drugs)
- When the sponsor requires the list of attendees.

Review the confidentiality guidelines in Appendix 1 of the Procedures for Reimbursement Reviews to understand how sponsor-provided information is managed.

4.4.2.2. Sending the Meeting Invitations

Once the list of attendees has been confirmed, please send the meeting invitation directly to the individuals identified.

4.4.2.3. Uploading Meeting Materials

Sponsors are provided with a secure portal (the Pharmaceutical Submissions SharePoint site) to upload confidential meeting materials for presubmission meetings and pipeline meetings. Please follow the instructions outlined in the Pharmaceutical Submissions SharePoint Site Set-Up Guide for details on requesting access to the site. Meeting materials must be uploaded to the Pharmaceutical Submissions SharePoint site in the location assigned for the meeting. Sponsors should request access to the Pharmaceutical Submissions SharePoint site 10 business days prior to the intended date of uploading the meeting materials. If this timeline cannot be met, please contact support@cda-amc.ca as soon as possible to ensure the meeting materials can be submitted without delay.

4.4.2.4. Participation in the Meetings

At meetings organized by Health Canada, CDA-AMC will observe the presentations and discussions. Sponsors with questions regarding the reimbursement review process should arrange a presubmission meeting to have a detailed discussion about the pending application.

5. Application Scope

Guidance for defining the population, intervention, comparators, outcomes, clinical evidence, and economic evidence for the application are provided within this section. Sponsors who have questions about the scope of the application and/or any of the application requirements are encouraged to contact CDA-AMC well in advance of the target filing date to seek clarification. Sponsors can provide written questions to CDA-AMC and participate in a presubmission meeting to have a detailed discussion about the pending application.

Deviations from the required scope must be discussed with, and accepted by, CDA-AMC in advance of filing the application. Please submit the inquiry form with complete details of any proposed deviations from the requirements to the Pharmaceutical Submissions SharePoint Site.

5.1. Initial Submissions

5.1.1. Population

The population for the systematic literature review and pharmacoeconomic evaluation will be defined as the full population identified in the approved and/or proposed Health Canada indication for which the sponsor is submitting (unless otherwise decided on in consultation with CDA-AMC). While a sponsor's reimbursement request may be specific to a subgroup or subpopulation of patients within the Health Canada indication, the population defined in the systematic review protocol will typically not be limited to the reimbursement request.

The subpopulations identified in the sponsor's reimbursement request should be prespecified in the protocol as a subgroup(s) of interest and the results reported where available. Other relevant subgroups that are likely to be of interest to clinicians, drug plans, patients, and those included in the sponsor's pharmacoeconomic submission should also be included in the protocol. These should be based on clinically important prognostic factors, confounders, or modifiers of treatment effects.

5.1.2. Intervention

The intervention will be specified as the drug, formulation, and route of administration under review, and within the Health Canada–approved dosage range. For studies that include multiple intervention arms with differing dosages, only those arms with dosages within the Health Canada–approved range should be included in the systematic review. For pre-NOC submissions, where there is uncertainty about which doses will be approved by Health Canada, all dosage arms should be included.

5.1.3. Comparator(s)

5.1.3.1. Standard and Complex Reviews

All relevant comparators must be included in the systematic literature review, pharmacoeconomic evaluation, and budget impact analysis, unless the sponsor has discussed with CDA-AMC and received formal notification that 1 or more relevant comparators may be excluded. Relevant comparators include any of the following:

- treatments currently reimbursed by at least 1 participating drug plan for the indication under review
- reimbursed treatments that are currently used off-label in practice in Canada
- treatments that have previously received a recommendation in favour of reimbursement from CDA-AMC for the indication under review.

The review will typically focus on drug comparators that are reimbursed by public drug plans. Though not typical, in some circumstances nondrug comparators (e.g., transfusion, plasmapheresis) may also be

included as comparators. Comparators not approved by Health Canada for the indication under review may also be considered relevant if they are the standard of care and their use is reimbursed by drug programs for the indication of interest. Comparators available through Health Canada's Special Access Program for the indication under review may also be considered.

5.1.3.2. PACES Tailored Reviews

Comparators in the Clinical Submission Template

All relevant comparators should typically be included in the systematic literature review, pharmacoeconomic evaluation, and budget impact analysis unless the sponsor has discussed with CDA-AMC and received formal notification that 1 or more relevant comparators may be excluded. Relevant comparators include any of the following:

- treatments currently reimbursed by at least 1 participating drug plan for the indication under review
- reimbursed treatments that are currently used off-label in practice in Canada
- treatments that have previously received a recommendation in favour of reimbursement from CDA-AMC for the indication under review.
- For some PACES applications, CDA-AMC may be willing to accept a clinical submission that is focused on a direct or indirect comparison of the drug under review versus a narrower list of appropriate comparators. As noted in the eligibility criteria for the PACES process, this would typically be considered when the sponsor is comparing against a drug with the same indication, in the same therapeutic classification based on the 4th level of the Anatomic and Therapeutic Classification (ATC) System, and with the same mechanism of action.

Comparators in Economic Submission Materials

When completing the economic submission requirements for a PACES tailored review, the sponsor must include all relevant comparators in the cost table and within the budget impact analysis.

5.1.3.3. New Product Variation Tailored Review

Comparators in the Clinical Section of the Submission Template

The clinical comparator for a new product variation tailored review will typically be 1 of the following:

- For a new combination product, the comparator is typically the individual components of the product used separately.
- For a new formulation of an existing drug, the comparator is typically the existing formulation of the drug that would be displaced by the introduction of the new formulation (e.g., a subcutaneous formulation would replace an IV formulation).

Comparators in the Economic Section of the Submission Template

When completing the economic sections of the tailored review submission template, the sponsor must include all relevant comparators in the cost table and within the budget impact analysis.

5.1.4. Outcomes

The end points included in the systematic literature review should reflect those studied in the clinical development program for the drug review. This includes, but is not limited to:

- all primary end points in clinical studies
- all secondary end points in clinical studies
- any end points included in the economic evaluation
- health-related quality of life end points (irrespective of classification within the hierarchy of end points in the trial protocol).

5.1.5. Clinical Evidence

5.1.5.1. Complex Reviews

Pivotal Trials and RCT Evidence

In addition to the clinical trials submitted as pivotal studies to Health Canada, other phase III or IV RCTs should be included in the systematic review. Consideration may be given to including other study designs in the protocol-selected studies on a case-by-case basis (e.g., if the pivotal trials are not phase III RCTs).

Indirect Comparison

Sponsors may file indirect comparisons to demonstrate the comparative clinical efficacy of the drug under review versus appropriate comparators. By default, CDA-AMC will typically allow sponsors to submit 1 of these comparisons for a given combination of patient population, comparator, and end point. The aim is to minimize the submission of redundant comparisons while providing sponsors flexibility to submit the analyses they consider most likely to provide valid effect estimates. Sponsors who wish to provide additional comparisons for a given combination of patient population, comparator, and end point will need to consult with CDA-AMC during the presubmission phase.

Long-Term Extension Data

The sponsor may submit evidence from long-term extension studies. The sponsor must ensure that all source documentation, including the clinical study report (if available), are included in the application materials. If data from long-term extension studies are not available at the time of filing the application, this should be noted within the applicable section of the clinical submission template (i.e., do not delete that section if there are no data available).

Studies Addressing Gaps in the Pivotal and RCT Evidence

For an application to be reviewed through the complex process, the sponsor may submit summarized evidence from additional studies that address important gaps in the evidence from the pivotal clinical trial(s), RCT(s), and direct or indirect comparative effectiveness and/or safety evidence. Sponsors must clearly identify the gaps in the evidence. Justification for the inclusion of real-world evidence must be provided; this should cover, as relevant, the reasons for the absence of randomized evidence, the limitations of existing trials, and the ability to produce meaningful real-world evidence for the specific research question.

5.1.5.2. Standard Reviews

Pivotal Trials and RCT Evidence

In addition to the clinical trials submitted as pivotal studies to Health Canada, other phase III or IV RCTs should be included in the systematic review. Consideration may be given to including other study designs in the protocol-selected studies on a case-by-case basis (e.g., if the pivotal trials are not phase III RCTs).

Indirect Comparison

Sponsors may file indirect comparisons to demonstrate the comparative clinical efficacy of the drug under review versus appropriate comparators. By default, CDA-AMC will typically allow sponsors to submit 1 of these comparisons for a given combination of patient population, comparator, and end point. The aim is to minimize the submission of redundant comparisons while providing sponsors flexibility to submit the analyses they consider most likely to provide valid effect estimates. Sponsors who wish to provide additional comparisons for a given combination of patient population, comparator, and end point will need to consult with CDA-AMC during the presubmission phase.

Long-Term Extension Data

The sponsor may submit evidence from long-term extension studies. The sponsor must ensure that all source documentation, including the clinical study report (if available), are included in the application materials. If data from long-term extension studies are not available at the time of filing the application, this should be noted within the applicable section of the clinical submission template (i.e., do not delete that section if there are no data available).

Studies Addressing Gaps in the Pivotal and RCT Evidence

Evidence from additional studies that address important gaps in the evidence from the pivotal trials, RCTs, and long-term extension phase studies **is not accepted** for standard review applications. As summarized in Table 17, sponsors with applications that do not meet the complex review criteria specified in scenarios 1 to 4 may still include evidence from additional studies in their application; however, the applications will be subject to a Schedule E application fee and would not have the additional process enhancements outlined in the complex review process, except for the review and

recommendation phases including consideration of the additional evidence. This must be confirmed with CDA-AMC before filing the application.

5.1.5.3. PACES Tailored Reviews

Pivotal Trials and RCT Evidence

In addition to the clinical trials submitted as pivotal studies to Health Canada, other phase III or IV RCTs should be included in the systematic review. Consideration may be given to including other study designs in the protocol-selected studies on a case-by-case basis (e.g., if the pivotal trials are not phase III RCTs).

Indirect Comparison

Sponsors may file indirect comparisons using selected methodologies to demonstrate the comparative clinical efficacy of the drug under review versus appropriate comparator(s). Specifically, the following forms of indirect comparison will be acceptable for the PACES review process:

- indirect comparative evidence that is based on aggregate clinical trial data (e.g., a mixed treatment comparison network meta-analysis)
- a single anchored MAIC.

Sponsors with any other forms of indirect evidence (e.g., unanchored MAIC) must file the application through the standard review process. Please note that other forms of indirect comparison may be more appropriate for the sponsor to provide evidence of the comparative clinical efficacy of the drug under review. The eligibility criteria for the PACES tailored review process should not be considered advice concerning the most appropriate methodology for indirect comparison and the choice of methodology rests solely with the sponsor. Before a review is initiated, CDA-AMC will not conduct preliminary evaluations of the sponsor's indirect comparison to advise on methodology.

By default, CDA-AMC will typically allow sponsors to submit 1 of these comparisons for a given combination of patient population, comparator, and end point. The aim is to minimize the submission of redundant comparisons while providing sponsors flexibility to submit the analyses they consider most likely to provide valid effect estimates. Sponsors who wish to provide additional comparisons for a given combination of patient population, comparator, and end point will need to consult with CDA-AMC during the presubmission phase.

Long-Term Extension Data

Evidence from long-term extension phase studies **is not accepted** for tailored review applications.

Studies Addressing Gaps in the Pivotal and RCT Evidence

Evidence from additional studies that address important gaps in the evidence from the pivotal trials, RCTs, and long-term extension phase studies **is not accepted** for tailored review applications.

5.1.5.4. Product Variation Tailored Reviews

Pivotal Trials and RCT Evidence

The sponsor must submit evidence from the clinical trials submitted as pivotal studies to Health Canada.

Indirect Comparison

Evidence from indirect comparisons **is not accepted** for product variation tailored reviews.

Long-Term Extension Data

Evidence from long-term extension phase studies **is not accepted** for product variation tailored reviews.

Studies Addressing Gaps in the Pivotal and RCT Evidence

Evidence from additional studies that address important gaps in the evidence from the pivotal trials, RCTs, and long-term extension phase studies **is not accepted** for product variation tailored reviews.

5.1.6. Economic Evidence

5.1.6.1. Standard and Complex Reviews

Sponsors must submit either a cost-utility analysis or cost-minimization analysis (refer to sections 6.6.1 and 6.6.2, respectively).

5.1.6.2. PACES Tailored Reviews

Sponsors will complete an appendix summarizing the key components of the economic evaluation and must submit the pharmacoeconomic submission requirements for cost-minimization analyses (refer to section 6.6.2).

5.1.6.3. Product Variation Tailored Reviews

Sponsors will complete the economic evidence section of the tailored review submission template. There is no opportunity for the submission of supplemental economic evidence.

5.2. Resubmissions

5.2.1. Population

The population for a resubmission is typically aligned with the indication previously submitted for review by CDA-AMC; however, in select cases the sponsor may request the resubmission focus on a subpopulation. CDA-AMC will evaluate these requests on a case-by-case basis with the sponsor.

5.2.2. Intervention

The intervention for a resubmission is typically aligned with the product that was previously submitted for review by CDA-AMC (though the application may be updated to include new dosage formats or strengths as required).

5.2.3. Comparator(s)

All relevant comparators should be included unless the sponsor has discussed with CDA-AMC and received formal notification that 1 or more relevant comparators may be excluded. The relevant comparators must reflect the treatment paradigm and reimbursement status at the time of filing the resubmission application and cannot be limited only to those that were relevant at the time of the initial submission.

5.2.4. Outcomes

The sponsor should ensure that the outcomes reflect those that were identified as clinically important in the initial submission.

5.2.5. Clinical Evidence

The clinical evidence for a resubmission will typically require 1 or more new studies that address specific issues identified by the expert committee in the final recommendation document. Evidence from a new study may not be required for a resubmission if the reimbursement request is for a subpopulation of patients from the initial submission and all relevant evidence to support the benefit of the subpopulation was included within the broader evidence reviewed during the initial submission. This means that CDA-AMC will review previously submitted evidence in the context of a new reimbursement request, without requiring new clinical evidence.

5.2.6. Economic Evidence

In general, sponsors must submit either a cost-utility analysis or cost-minimization analysis (refer to sections 6.6.1 and 6.6.2, respectively). CDA-AMC applies a proportionate approach to resubmissions and waives an economic evaluation if the new clinical evidence submitted is not expected to alter the base case of the economic evaluation that was reviewed during the initial submission.

5.3. Reassessments

5.3.1. Population

The reassessment will be conducted in a manner that is “fit for purpose” with applications tailored to address the decision problem, as shown in Table 4.

5.3.1.1. Reassessment That Is Not for a Time-Limited Reimbursement Recommendation

The systematic literature review and pharmacoeconomic evaluation should focus on the population that is relevant to the sponsor's request for revised reimbursement criteria for the drug under review.

5.3.1.2. Reassessment for a Time-Limited Recommendation

The reassessment of a time-limited recommendation will focus on the indication that was previously reviewed by CDA-AMC. This is typically the full population identified in the Health Canada–approved indication, unless the sponsor received approval to file for a more restrictive population or an unlabeled indication. As outlined in Table 4, for a time-limited recommendation, sponsors may request revised reimbursement criteria as part of the reassessment process (e.g., modifications to initiation, renewal, discontinuation, or prescribing criteria). Sponsors who want to have additional populations addressed within the reassessment should contact CDA-AMC. These requests will be addressed on a case-by-case basis and may require the sponsor to file multiple applications and/or be subject to multiple application fees.

Table 4: Scope of Clinical and Economic Review for a Reassessment

Sponsor request	Clinical review	Economic review
Reassessment that is not for a time-limited reimbursement recommendation		
Sponsor seeking revisions to existing reimbursement criteria (e.g., expansion of the patient population)	Updated systematic literature review and indirect comparisons (if applicable)	Updated pharmacoeconomic evaluation that addresses the population that is relevant to the sponsor's request for revised reimbursement criteria
Reassessment that is for a time-limited reimbursement recommendation		
Sponsor is not seeking any revisions to the existing reimbursement criteria	Review of clinical evidence will be focused on the new evidence generated to address the gaps that were identified in the initial recommendation	Updated pharmacoeconomic evaluation that addresses the currently reimbursed population
Sponsor seeking revisions to existing reimbursement criteria (e.g., expansion of the patient population)	Updated systematic literature review and indirect comparisons (if applicable)	Updated pharmacoeconomic evaluation that addresses both: • the currently reimbursed population • the population that is relevant to the sponsor's request for revised reimbursement criteria

5.3.2. Intervention

The intervention for a resubmission is typically aligned with the product that was previously submitted for review by CDA-AMC (though the application may be updated to include new dosage formats or strengths as required).

5.3.3. Comparator(s)

All relevant comparators should be included unless the sponsor has discussed with CDA-AMC and received formal notification that 1 or more relevant comparators may be excluded. The relevant comparators must reflect the treatment paradigm and reimbursement status at the time of filing the reassessment application and cannot be limited only to those that were relevant at the time of the initial submission.

5.3.4. Outcomes

For the reassessment of a time-limited reimbursement recommendation, the outcomes of interest in the sponsor's application should reflect those that were studied in the phase III clinical trial and identified as important gaps in the evidence by the expert committee. This may include surrogate end points if, in the initial recommendation, the expert committee concluded that additional surrogate data would address uncertainty with the clinical evidence.

5.3.5. Clinical Evidence

5.3.5.1. Reassessment That Is Not for a Time-Limited Reimbursement Recommendation

The reassessment must include 1 or more new clinical studies that support the sponsor's request for revised reimbursement criteria for the drug or the sponsor must be providing the reassessment to address the conditions in a time-limited reimbursement recommendation.

5.3.5.2. Reassessment for a Time-Limited Recommendation

For the reassessment of a time-limited reimbursement recommendation, the focus of the reassessment application must be on the updated data from the phase III trial. Consideration may be given to including other study designs on a case-by-case basis (e.g., real-world evidence generated to address additional gaps in the evidence); however, this evidence must be provided in addition to the phase III trial data and will not be accepted as a substitute for the phase III trial evidence.

5.3.6. Economic Evidence

5.3.6.1. Reassessment That Is Not for a Time-Limited Reimbursement Recommendation

The reassessment must include an updated pharmacoeconomic evaluation that addresses the population that is relevant to the sponsor's request for revised reimbursement criteria.

5.3.6.2. Reassessment for a Time-Limited Recommendation

As outlined in Table 4, the economic evaluation for the reassessment will depend on whether the sponsor is requesting revisions to the existing reimbursement criteria when filing the application. If the sponsor is not requesting changes to the reimbursement criteria, they must provide an updated pharmacoeconomic evaluation that addresses the currently reimbursed population. If the sponsor is seeking revisions to the existing reimbursement, they must submit a pharmacoeconomic evaluation that addresses both the currently reimbursed population and the population that is relevant to the sponsor's request for revised reimbursement criteria.

6. Application Requirements

This section provides details regarding the documentation that must be filed and accepted before a reimbursement review is initiated.

- The clinical and pharmacoeconomic information provided by the sponsor should focus on the indication(s) to be reviewed (unless otherwise specified).
- Sponsors must use the templates that are hyperlinked throughout this section whenever applicable (these are also available on the website).
- Checklists are available in Appendix 4 to assist sponsors in ensuring that all required documentation has been included in their application. To expedite screening and for efficient use of documents throughout the review, sponsors must organize all documents in the order described subsequently and follow the file folder format in Appendix 5.
- Table 5 summarizes the application requirements submissions, resubmissions, and reassessments. The typical application requirements for a resubmission or reassessment are summarized in Table 5. Sponsors seeking a waiver of any requirements must contact CDA-AMC with a complete list of all the relevant requirements with a rationale for why they should not be included in the application.
- CDA-AMC applies a fit-for-purpose approach when determining eligibility and the application requirements for a resubmission or reassessment. Certain application requirements may be waived if they are not deemed relevant by CDA-AMC (e.g., an economic evaluation could be waived if the new clinical evidence submitted is not expected to alter the base case of the economic evaluation that was reviewed during the initial submission).
- Whenever relevant, the specific requirements for a submission filed on a pre-NOC versus a post-NOC basis are delineated in the description.
- The sponsor is responsible for ensuring that appropriate copyright permissions have been obtained for copies of the articles that will be shared among CDA-AMC, the expert committee, and the drug programs.

Table 5: Application Requirements

Specific items and criteria	Standard Review	Product Variation Tailored Review	PACES Tailored Review	Complex Review	Resubmission or Reassessment
General Information					
Application overview template	Required	Required	Required	Required	Required
Executive summary template	Required	Required	Required	Required	Required
Product monograph	Required	Required	Required	Required	Required
Completed declaration letter template	Required	Required	Required	Required	Required
Completed regulatory and HTA status template	Required	Required	Required	Required	Required
Request for deviation response letter or statement that a deviation was not requested	Required	Not Applicable	May be required	Required	Required
Submission Template					
Complete summary of clinical evidence template	Required	Not Applicable	Not Applicable	Required	Required
Completed tailored review submission template	Not Applicable	Required	Required	Not Applicable	Not Applicable
RIS file with references	Required	Required	Required	Required	Required
Health Canada Documentation					
Letter of Undertaking (if NOC/c)	Required	Not Applicable	Not Applicable	Required	Not required
Table of Clarimails or Clarifaxes	Required	Required	Required	Required	Not required
Efficacy, Effectiveness, and Safety Information					
Common Technical Document sections 2.5, 2.7.3, 2.7.4, and 5.2, or a statement indicating any section(s) that are not available	Required	Required	Required	Required	Required
Clinical study reports for pivotal and key studies	Required	Required	Required	Required	Required

Specific items and criteria	Standard Review	Product Variation Tailored Review	PACES Tailored Review	Complex Review	Resubmission or Reassessment
Reference list, copies of key studies, and errata	Required	Required	Required	Required	Required
Table of studies	Required	Required	Required	Required	Required
Reference list and articles for validity of outcome measure	Required	Not required	Not required	Required	May be required
Indirect comparison with full technical report	May be required	Not required	May be required	May be required	May be required
Economic Information					
Pharmacoeconomic evaluation	Required	Not required	CMA Required	Required	Required[1]
Unlocked and fully executable economic model	Required	Not required	CMA Required	Required	Required[1]
Economic model supporting documentation	Required	Not required	Required	Required	Required[1]
Completed checklist of economic requirements	Required	Required	Required	Required	Required[1]
RIS file with economic references	Required	Not required	Required	Required	Required[1]
Budget Impact Analysis					
Aggregate pan-Canadian budget impact report	Required	Required	Required	Required	Required
Aggregate pan-Canadian budget impact model	Required	Required	Required	Required	Required
Supporting documentation	Required	Required	Required	Required	Required
Pricing and Distribution Information					
Submitted price per smallest dispensable unit to 4 decimal places	Required	Required	Required	Required	Required
Method of distribution	Required	Required	Required	Required	Required
Reimbursement Status					
Reimbursement status of relevant comparators	Required	Required	Required	Required	Required

Specific items and criteria	Standard Review	Product Variation Tailored Review	PACES Tailored Review	Complex Review	Resubmission or Reassessment
Provisional algorithm (only for oncology drugs)					
Place in therapy template	Required	Not required	Required	Required	Required
Reference list and copies of studies	Required	Not required	Required	Required	Required
Companion diagnostics					
Reference list and articles for clinical utility	May be required	Not required	Not required	May be required	May be required
Disclosable price	May be required	Not required	Not required	May be required	May be required
Implementation					
Completed implementation plan template	Not required	Not required	Not required	Required for cell and gene therapies	Not required
Pre-NOC Letter					
Letter for finalized indication	Required	Required	Required	Required	N/A

[1] CDA-AMC applies a proportionate approach to resubmissions and waive an economic evaluation if the new clinical evidence submitted is not expected to alter the base case of the economic evaluation that was reviewed during the initial submission).

NOC/c = notice of compliance of conditions; PACES = pharmaceuticals with anticipated comparable efficacy and safety

6.1. General Information

6.1.1. Application Overview Template

A completed application overview template.

6.1.2. Executive Summary

A high-level summary of the application using the executive summary template available on the CDA-AMC website. The document must be referenced and must not exceed 5 (excluding references).

6.1.3. Product Monograph

Sponsors must provide immediate notification, up until the time that the final recommendation is issued of any changes to the Health Canada–approved product monograph for the drug under review and provide a revised copy. Failure by the sponsor to inform CDA-AMC of any changes to the product monograph could result in a temporary suspension of the review.

Following notification of changes to the product monograph, the nature and extent of the changes will be assessed and the timelines required for review and, if necessary, incorporate the changes into the review report will be determined. This could result in the review timelines being delayed, including the submission being considered at a later meeting of the expert committee or a delay in issuing the final recommendation. The sponsor will be notified of any revisions to the anticipated timeline for the review, deferral by the expert committee, or the subsequent recommendation not reflecting the most currently available product monograph information relating to the drug under review.

Requirements regarding the product monograph for a submission filed on a pre-NOC basis:

- At the time of filing the submission: a copy of the most recent draft product monograph showing the company, drug brand, and non-proprietary names that correspond to the anticipated NOC
- As soon as available:
- a copy of the draft product monograph showing, in tracked changes, all the clinical and label review changes made up to the time of the product monograph being approved by Health Canada (if there are no changes to the draft product monograph initially filed, other than the date on the product monograph, please include a placeholder document indicating this)
- a copy of the clean and dated product monograph approved by Health Canada.

Requirements regarding the product monograph for a submission filed on a post-NOC basis:

- A copy of the most current version of the Health Canada–approved product monograph

6.1.4. Declaration Letter

A letter from the holder of the NOC or NOC/c (or from the sponsor applying for an NOC, in the case of a submission filed on a pre-NOC basis), using the declaration letter template, printed on company letterhead, and signed by an appropriate senior official.

6.1.5. Regulatory and HTA Status in Other Jurisdictions

At the time of filing of the application, a completed template summarizing the status of the drug under review at selected regulatory and health technology assessment (HTA) agencies. The sponsor is required to provide an updated copy of the template to reflect any changes in the status (if applicable) when the sponsor provides their comments on the draft report. This document must be provided as a Microsoft Word document.

6.1.6. Request for Deviation from Application Scope and/or Pharmacoeconomic Requirements

All sponsors that file a request for deviation must include a copy of the decision letter within the General Information section of the application. Sponsors are required to include a copy of the letter from irrespective of the decision regarding whether the deviation has been accepted. If the sponsor has not filed a request for deviation, we request that they please include a placeholder document stating that no request for deviation was filed. Sponsors are reminded that deviations from any of the requirements must be discussed with and accepted in advance of filing the application. Failure to seek advanced approval of the deviation may result in an extension of the screening timelines.

6.2. Sponsor Submission Templates

6.2.1. Clinical Evidence Template for Standard and Complex Reviews

Sponsors filing a standard or complex review are required to complete the sponsor summary of clinical evidence template in accordance with the instructions provided in the template.

6.2.2. RIS File With References

The sponsor must provide a RIS file containing the references used in the report. A RIS file is a standardized bibliographic format that enables citation management programs to exchange documents. The file should be named in accordance with the instructions in Appendix.

6.2.3. Submission Templates for Tailored Reviews

A completed tailored review submission template.

6.2.4. RIS File With References

The sponsor must provide a RIS file containing the references used in the submission template. A RIS file is a standardized bibliographic format that enables citation management programs to exchange documents. The file should be named in accordance with the instructions in Appendix.

6.3. Health Canada Documentation

6.3.1. Clarimails or Clarifaxes

Requirements regarding Clarimails/Clarifaxes for a submission filed on a pre-NOC basis:

- At time of filing the submission: a summary table of Clarimails/Clarifaxes relating to any clinical aspects of the Health Canada review of the drug (e.g., clinical studies or product monograph, not chemistry- and manufacturing-related topics) up to the time of filing; including the date of each Clarimail/Clarifax, the topic for clarification, a brief summary of the response, and the date of the response must be included.
- On an ongoing basis up to the point of the NOC or NOC/c being issued, the sponsor must provide revised summary tables to reflect any additional Clarimails/Clarifaxes as aforementioned.

Requirements regarding Clarimails/Clarifaxes for a submission filed on a post-NOC basis:

- A summary table of Clarimails/Clarifaxes relating to any clinical aspects of the Health Canada review of the drug (e.g., clinical studies or product monograph, not chemistry- and manufacturing-related topics) up to the point of the NOC or NOC/c being issued; including the date of each Clarimail/Clarifax, the topic for clarification, a brief summary of the response, and the date of the response must be included.

6.4. Efficacy, Effectiveness, and Safety Evidence

6.4.1. Common Technical Document

A copy of the following Common Technical Document sections is required.

- 2.5 Clinical Overview
- 2.7.3 Summary of Clinical Efficacy
- 2.7.4 Summary of Clinical Safety
- 5.2 Tabular Listing of All Clinical Studies

If any of these sections of the Common Technical Document were not a requirement for filing the regulatory submission with Health Canada, a placeholder document with a statement confirming this is required.

6.4.2. Clinical Study Reports

Clinical study reports must be provided for the pivotal trials as well as any other studies that address key clinical issues. The clinical study reports should be provided in full and include both the complete study protocol and analysis plan. If a Clinical Study Report is unavailable to the sponsor, a placeholder document with a statement confirming this is required.

6.4.3. Publications or Manuscripts for Key Clinical Studies

For the clinical studies requirements, the preference is for any unpublished data to be submitted in manuscript format; however, if the data are unavailable in manuscript format, the information should be provided in accordance with the CONSORT 2010 Statement Checklist, using clearly labelled sections (i.e., title, abstract, introduction, methods, results, discussion, other information). Please note that information submitted only as conference abstracts and/or posters will not be accepted for review.

Should an unpublished study submitted become published during the review process, the sponsor must provide a copy of the published study using the “2. Submission Files” folder on the Pharmaceutical Submissions SharePoint site. Depending on the nature of the information, the timelines required to review it and incorporate it into the review report will be determined. This could result in the submission being considered at a later expert committee meeting. The sponsor will be apprised of any revisions to the anticipated timelines for the review.

Requirements for an Initial Submission

- Copies of the published and unpublished studies that address key clinical issues for the drug under review.
- Copies of any supplemental appendices that are associated with published studies.
- Copies of any errata related to any of the published studies provided (or a placeholder document with a statement confirming that there are no errata).
- A reference list with all of the published and unpublished studies (including any errata) that address key clinical issues for the drug under review.

Requirements for a Resubmission

- Copies of the published and unpublished studies that address key clinical issues for the drug under review, including all new clinical information that addresses specific issues identified by the expert committee in the final recommendation document.
- Copies of any supplemental appendices that are associated with published studies.
- Copies of any errata related to any of the published studies provided (or a placeholder document with a statement confirming that there are no errata).
- A reference list with all the published and unpublished studies (including any errata) that address key clinical issues for the drug under review. The studies in the list must be presented as follows:

- All new clinical information that addresses specific issues identified by the expert committee in the final recommendation document.
- Key clinical studies that were included in the initial submission and/or previous resubmissions filed.

Requirements for a Reassessment

- A reference list of the published and unpublished studies included in the submission; the list should specifically identify the new clinical information that supports the sponsor's request for the reassessment (e.g., revised reimbursement criteria).
- Copies of any errata related to any of the published studies provided (or a placeholder document with a statement confirming that there are no errata).

6.4.4. Table of Studies

A tabulated list of all published and unpublished clinical studies using the table of studies template must be provided. This table may be provided as a Microsoft Word or PDF document.

Any data (e.g., pre-planned analyses of primary outcome measures) for a planned or ongoing clinical study included in the "table of studies" requirement that becomes available during the review process must be provided as soon as possible using the "2. Submission Files" folder on the Pharmaceutical Submissions SharePoint site. The information will be assessed upon receipt and the timelines required to review it and incorporate it into the review report will be determined. This could result in the submission being considered at a later meeting of the expert committee. The sponsor will be notified of any revisions to the anticipated timelines for the review.

6.4.5. Validity of Outcome Measures

A reference list and copies of references supporting the validity of primary outcome measures in clinical studies. If no references are available, a placeholder document is required with a statement confirming that a search was undertaken but no references were located.

6.5. Indirect Comparisons

Sponsors are required to provide copies of any indirect comparisons that were used in their pharmacoeconomic evaluation. In addition, sponsors may elect to provide one or more indirect comparisons to provide evidence of the comparative safety and efficacy of the drug under review relative to appropriate comparators. The indirect comparisons must be provided as a separate report in the submission package.

CDA-AMC will allow sponsors to submit 1 indirect comparison for a given combination of patient population, comparator, and end point. If there are multiple analyses for separate patient populations, separate sets of comparators, or separate end points, they can be accepted. The aim is to minimize the

submission of redundant comparisons and encourage sponsors to submit the analysis they consider most likely to provide a valid effect estimate. Sponsors that wish to provide additional comparisons for a given combination of patient population, comparator, and end point must consult with CDA-AMC prior to submission.

6.6. Pharmacoeconomic Submission

The pharmacoeconomic submission for a standard review, complex review, resubmission, or reassessment consists of:

- a technical report of the pharmacoeconomic evaluation
- an economic model (for a cost-utility analysis) or cost calculations (for a cost-minimization analysis)
- a technical report of the budget impact analysis (BIA)
- a budget impact model
- a completed checklist indicating that the economic requirements have been met
- any supporting material relevant to the pharmacoeconomic submission.

The technical reports of the pharmacoeconomic evaluation and BIA must be consistent with the economic model and budget impact model, respectively. In both cases, all scenario analyses presented in the technical reports must be replicable in the submitted models. Any submitted models cannot require CDA-AMC to agree to terms and conditions or have a legal disclaimer. Models that require the user to review and agree to terms and conditions and/or acknowledge a legal disclaimer added by the vendor or sponsor will not be accepted for review. Any sponsors who have questions regarding the inclusion of a disclaimer should contact CDA-AMC prior to filing the application.

The economic submission (pharmacoeconomic evaluation and model) should be undertaken in accordance with the Guidelines for the Economic Evaluation of Health Technologies: Canada (4th edition) and supporting documents (as referred to on the guidelines landing page) which provide guidance on best practices for undertaking economic evaluations within the health care setting in Canada.

When multiple indications and/or populations are relevant, CDA-AMC will assess whether the review constitutes multiple submissions or may require multiple application fees. Please refer to the *Fee Schedule for Pharmaceutical Reviews* for details.

The specific requirements described in the sections that follow must be met when submitting to the reimbursement review processes. A summary is provided in Appendix 5.

The preferred approach for the pharmacoeconomic analysis is a cost-utility analysis. In some specific situations, a cost-minimization analysis could be submitted, but the sponsor is asked to review the criteria in the cost-minimization section carefully (refer to section 6.6.2).

Only 1 type of economic evaluation can be included in an application. For example, the following will not be accepted:

- including more than one economic model for the review of a single indication;
- submitting both a cost-minimization analysis and cost-utility analysis for the review of a single indication.

The sponsor is required to include a completed economic requirements checklist within their application package. This checklist is required to ensure that the sponsor is undertaking a quality check of their application to minimize delays in the screening process.

6.6.1. Cost-Utility Analysis

6.6.1.1. Pharmacoeconomic Evaluation: Technical Report

Target Population

Unless otherwise specified in section 5, or a deviation was accepted by CDA-AMC, the base-case analysis must reflect the Health Canada–approved indication for which the drug is being submitted. If a sponsor is requesting reimbursement for a specific subgroup of the indicated population or there are any relevant subgroups, these must be provided as scenario analyses. For submissions filed on a pre-NOC basis, where the approved NOC indication differs from the anticipated indication for which the pharmacoeconomic evaluation was conducted, the review may be suspended until a revised pharmacoeconomic submission reflecting the approved indication is provided.

For reassessments, the base-case analysis must reflect the scope of the reassessment:

- If the reassessment is focused on proposed revisions to the existing reimbursement criteria for the drug under review, the base-case analysis must reflect the target population that would be covered under the revised reimbursement criteria that have been proposed by the sponsor.
- If the reassessment is focused on validation of the existing reimbursement criteria for the drug under review, the base-case analysis must be focused on the population which is currently covered under the current reimbursement criteria.
- If there are any relevant subgroups, these must be provided as scenario analyses.

Comparators

The base case must include all relevant comparators as described in section 5.

If the sponsor submits a different reimbursement request, all relevant comparators must be included in that scenario analysis.

Missing comparators may be identified during the screening phase and the application will not be accepted for review. However, in some situations, the absence of one or more relevant comparators may

not be apparent until the application has been accepted for review and initiated. In these cases, the sponsor will be notified regarding the deficiency and the timelines of the review may be affected (i.e., may result in the application being reviewed at a later meeting of the expert review committee).

Perspective

The base case must be from the perspective of the publicly funded health care payer. In certain cases, a societal perspective may be included as a second base case. Refer to section 9.2.2.4 for further details.

Discounting

If the time horizon is greater than 1 year, the base case must use a discount rate of 1.5% for both costs and quality-adjusted life-years.

Effectiveness

Composite outcomes are generally not satisfactory to inform treatment effect estimates. Sponsors should base their pharmacoeconomic evaluation on relevant individual outcomes. If composite outcomes are included in the pharmacoeconomic evaluation, the sponsor may be requested to include the individual outcomes during the review process. In this situation, the sponsor will be notified regarding the deficiency and the timelines of the review may be affected (i.e., may result in the application being reviewed at a later meeting of the expert review committee).

Costs and Resource Use

The specific drug price(s) submitted for the lowest dispensable unit (to 4 decimal places) must be used in the sponsor's base-case analysis. The unit cost(s) must be stated transparently within the model.

All submitted forms and strengths must be included in the submitted model.

Analysis

If more than 1 comparator is included, the results should be reported using a sequential analysis that indicates where the drug lies on the cost-effectiveness efficiency frontier.

- As referred to earlier in section 6.6, the Guidelines for the Economic Evaluation of Health Technologies: Canada (4th edition) and supporting documentation should be consulted for guidance on sequential and pairwise analyses.

The base-case analysis must be conducted probabilistically. The base-case analysis must be presented deterministically as well. Scenario analyses may be reported deterministically, but the pharmacoeconomic model must be programmed in such a way that allows them to be run probabilistically.

Reporting

The results of the sponsor's base case and scenario analysis for the reimbursement-requested population (if different from the base case) must be presented in a disaggregated manner before being aggregated.

A breakdown by costs (e.g., drug acquisition costs, administration costs, adverse event cost, health state costs), by life-years, and by quality-adjusted life-years (e.g., benefits generated in each health or event state, benefits generated during the trial period versus the extrapolation period), as relevant, must be reported based on the probabilistic results.

A suggested reporting format is presented in Table 6 and Table 7.

Table 6: Disaggregated Clinical Outcomes and Costs for a Cost-Utility Analysis

Parameter	Drug under review	Comparator #1	Comparator #2 (add as required)
Discounted life-years			
Total LYs			
By health state			
Health state 1			
Health state 2			
Discounted QALYs			
Total QALYs			
By health state			
Health state 1			
Health state 2			
Incremental QALYs generated within trial period			
Incremental QALYs generated after trial period			
Discounted costs			
Total costs			
Drug			
Administration			
Other resource costs			
Health state or event			
Add others (as required)			

QALY = quality-adjusted life-years; LY = life-years.

Table 7: Presentation of Sequential Incremental Cost-Utility Ratio for a Cost-Utility Analysis

Treatment	Cost	QALYs	Incremental cost per QALY gained	
			Versus reference	Sequential ICUR
Reference (Intervention A)				
Intervention B				
Intervention C				

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-years.

Companion Diagnostics

If there is a companion diagnostic test associated with the drug under review, the pharmacoeconomic evaluation (and model) must include relevant costs and consequences for these tests in relation to the drug under review (e.g., test costs for all patients in whom the drug under review is considered, costs from diagnostic information obtained and subsequent treatment decisions, rates of true- and false-positives and true- and false-negatives, and potential consequences of the test results). The source(s) and assumption(s) of the relevant inputs should be provided as well.

6.6.1.2. Economic Model

- An unlocked version of the economic model used to inform the technical report of the pharmacoeconomic evaluation must be provided.
- The economic model must be programmed in Excel. The sponsor must contact CDA-AMC in advance if considering alternative program software to ensure that it is acceptable and whether additional requirements will apply. The version of Excel must be clearly stated in the sponsor's technical report.
- The model must be able to function in a stand-alone environment that does not require access to a web-based platform.
- The sponsor must provide the model in its entirety, meaning CDA-AMC must have full access to the programming code (e.g., macros, Visual Basic for Applications [VBA] code) and be able to fully execute the model based on modifications to parameters of interest. CDA-AMC must be able to vary individual parameters, view the calculations, and run the model to generate results.

Probabilistic analysis must be stable over multiple model runs. A congruence test should be provided to identify the appropriate number of iterations required for convergence to be reached. Results from the congruence test should inform the number of simulations conducted in the base case and all scenario analyses. If the sponsor chooses to use seeding within the model, the functionality to easily revise or disable this feature must be included to allow CDA-AMC to verify the stability of the probabilistic analysis.

The probabilistic analysis must run all interventions that are being compared against each other simultaneously or be conducted in a way that ensures the same input parameter values are considered within each simulation and report the analysis results sequentially as relevant.

For submissions that use time-to-event (e.g., survival) data, the sponsor's model must be flexible to easily assess all parametric distributions tested by the sponsor (at minimum, distributions tested must include Weibull, Gompertz, exponential, log-normal, log-logistic, generalized gamma, and gamma, which must be provided as 1-piece distributions unless an appropriate rationale for a piecewise analysis has been provided by the sponsor. Additional methods may be used as relevant). If any of these distributions are not possible, an acceptable rationale for exclusion must be provided. The sponsor must include 1 graph for each outcome (e.g., progression-free survival, time-to-death, etc.) that is flexible to simultaneously present the observed Kaplan-Meier curves and all fitted distribution curves assessed by the sponsor for each treatment. The graph(s) must allow CDA-AMC to include and remove distributions and treatments to allow visual inspection of each distribution individually and comparatively as needed.

Details on how a cohort or individuals progress through the model must be transparently reported. For instance, if a Markov model is submitted, a Markov trace is required; if a model does not incorporate set cycles, event-time traces must be provided that records the sequence of events that occurred over the model's full-time horizon. The computation behind the traces must not be hard coded via VBA, but derived through formula. While a trace must be provided, if inclusion of a trace will impact the model run time such that it does not meet requirements, the trace does not need to be incorporated within the PSA.

The use of IFERROR statements modifies the output of a model file, masking errors and making it difficult to undertake a thorough appraisal of the model. IFERROR statements should not be used in the submitted economic model.

The submitted economic model must have a reasonable run time. If the model run time for the base-case analysis and key scenario analyses exceeds 1 business day (8 hours) it will be considered to be excessive and will not be accepted. The run time is determined by CDA-AMC based on our computing powers.

6.6.2. Cost-Minimization Analysis

6.6.2.1. Pharmacoeconomic Evaluation: Technical Report

The preferred approach for the pharmacoeconomic analysis is a cost-utility analysis. However, in some specific situations, a cost-minimization analysis (CMA) may be sufficient.

A sponsor is encouraged to submit a cost-minimization analysis in situations where the following conditions are met:

1. The drug represents an additional drug in a therapeutic class in which there is already a reimbursed drug for the same indication.

2. The drug under review demonstrates similar clinical effects (i.e., has at least equivalent effectiveness and/or efficacy and be equivalently or less harmful) compared to the most appropriate comparator(s), based on: 1 or more clinical studies that directly compared the drug under review to relevant comparator(s), or 1 or more indirect comparisons that allow for the comparison of the drug under review to relevant comparator(s).
3. Fulfils the criteria for the PACES process (refer to section 3.3.1).

As comparative efficacy and safety will be assessed within the review, the appropriateness of a cost-minimization analysis cannot be confirmed during the screening phase of the process. The decision to submit a cost-minimization analysis for the pharmacoeconomic evaluation therefore rests with the sponsor. If a sponsor elects to submit a cost-minimization analysis, it will be essential for the sponsor to have appropriate evidence to demonstrate how it has met the criteria above, and specifically that the drug and the relevant comparator(s) are comparable or equivalent in clinical effects.

The submission of a cost minimization analysis implies comparable/equivalent clinical effects; where this is not demonstrated, the sponsor should submit a cost-utility analysis.

Should sponsors elect to provide a cost-utility analysis after the initiation of a review accepted based on a cost-minimization analysis, the review will be suspended for as long as is required to allow the sponsor and CDA-AMC to accommodate a change in the modelling approach. This may delay the target committee meeting date and CDA-AMC will not be liable to refund any review fees.

If there is a companion diagnostic test associated with the drug under review that is different than those required for the comparator treatments, a cost-utility analysis must be submitted.

Target Population

Unless otherwise specified in section 5, or a deviation was accepted by CDA-AMC, the base-case analysis must reflect the Health Canada–approved indication for which the drug is being submitted. If a sponsor is requesting reimbursement for a specific subgroup of the indicated population or there are any relevant subgroups, these must be provided as scenario analyses. For submissions filed on a pre-NOC basis, where the approved NOC indication differs from the anticipated indication for which the pharmacoeconomic evaluation was conducted, the review may be suspended until a revised pharmacoeconomic submission that reflects the approved indication is provided.

For reassessments, the base-case analysis must reflect the scope of the reassessment:

- If the reassessment is focused on proposed revisions to the existing reimbursement criteria for the drug under review, the base-case analysis must reflect the target population that would be covered under the revised reimbursement criteria that have been proposed by the sponsor.
- If the reassessment is focused on validation of the existing reimbursement criteria for the drug under review, the base-case analysis must be focused on the population that is covered under the current reimbursement criteria.

- If there are any relevant subgroups, these must be provided as scenario analyses.

Comparators

The base case must include all relevant comparators as described in section 5.

If the sponsor submits a different reimbursement request, all relevant comparators must be included in that scenario analysis.

Missing comparators may be identified during the screening phase and the application will not be accepted for review. However, in some situations, the absence of one or more relevant comparators may not be apparent until the application has been accepted for review and initiated. In these cases, the sponsor will be notified regarding the deficiency, and the timelines of the review may be affected (i.e., may result in the application being reviewed at a later meeting of the expert review committee).

Perspective

The base case must be from the perspective of the publicly funded health care payer. In certain cases, a societal perspective may be included as a second base case. Refer to section 9.2.2.4 for further details.

Discounting

If the time horizon is greater than 1 year, the base case must use a discount rate of 1.5% for costs.

Costs and Resource Use

The specific drug price(s) submitted for the lowest dispensable unit (to 4 decimal places) must be used in the sponsor's base-case analysis. The unit cost(s) must be stated transparently within the model.

All submitted forms and strengths must be included in the submitted model.

Analysis

The base-case analysis should be conducted probabilistically. A deterministic analysis may be presented if a rationale to support the absence of parameter uncertainty is provided.

Reporting

The results of the sponsor's base case and scenario analysis for the reimbursement-requested population (if different from the base case) must be presented in a disaggregated manner before being aggregated. A breakdown by costs (e.g., drug acquisition costs, administration costs) must be reported based on the base case results (i.e., based on probabilistic [or deterministic] output, as justified within the submission).

A suggested reporting format is presented in Table 8.

Table 8: Disaggregated Costs for a Cost-Minimization Analysis

Parameter	Drug under review	Comparator #1	Comparator #2 (add as required)
Discounted costs			
Total costs			
Drug			
Administration			
Other resource costs			
Health state or event			
Add others (as required)			

6.6.2.2. Cost Calculations

An unlocked Excel workbook containing the cost calculations used to inform the technical report of the pharmacoeconomic evaluation must be provided.

The Excel workbook must be able to function in a stand-alone environment that does not require access to a web-based platform.

If the analysis is deterministic, all analyses should be easily traceable through formulas within the Excel worksheet. CDA-AMC should be able to fully execute the analysis based on modifications to parameters of interest. CDA-AMC must be able to vary individual parameters and run the analysis to generate results.

If the analysis is probabilistic:

- The sponsor must provide the model in its entirety, meaning that CDA-AMC must have full access to the programming code (e.g., macros, VBA code) and be able to fully execute the analysis based on modifications to parameters of interest. CDA-AMC must be able to vary individual parameters and run the analysis to generate results. The results of the analysis must be traceable via formulas not hard-coded based on VBA output.
- Results must be stable over multiple models runs. A congruence test should be provided to identify the appropriate number of iterations required for convergence to be reached. If the sponsor chooses to use seeding within the model, the functionality to easily revise or disable this feature must be included to allow CDA-AMC to verify the stability of the probabilistic analysis.
- If more than 1 comparator is included, the probabilistic analysis must run all comparators simultaneously or be conducted in a way that ensures the same input parameter values are considered within each simulation.

The use of IFERROR statements modifies the output of a model file, masking errors and making it difficult to undertake a thorough appraisal of the model. IFERROR statements should not be used in the submitted economic model.

The submitted economic model must have a reasonable run time. If the model run time for the base-case analysis and key scenario analyses exceeds 1 business day (8 hours) it will be considered to be excessive and will not be accepted. The run time is determined by CDA-AMC based on our computing powers.

6.6.3. Budget Impact Analysis

The following information on the BIA (technical report and model) apply to all submissions.

6.6.3.1. BIA: Technical Report

Target Population

Unless otherwise specified in section 5, or a deviation was accepted by CDA-AMC, the base-case analysis must reflect the Health Canada–approved indication for which the drug is being submitted. If a sponsor is requesting reimbursement for a specific subgroup of the indicated population or there are any relevant subgroups, these must be provided as scenario analyses. For submissions filed on a pre-NOC basis, where the approved NOC indication differs from the anticipated indication for which the pharmacoeconomic evaluation was conducted, the review may be suspended until a revised pharmacoeconomic submission reflecting the approved indication is provided.

For reassessments, the base-case analysis must reflect the scope of the reassessment.

Perspective

The base case must reflect a pan-Canadian (national) drug program perspective (excluding Quebec), which must be derived from the following subset of individual drug programs participating in the drug reimbursement review processes: British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland and Labrador, and the Non-Insured Health Benefits Program (if applicable). No other participating drug program should be included in the analysis. If the drug is being reviewed through the plasma protein review pathway, an analysis from the Canadian Blood Services perspective must also be provided.

Time Horizon

When forecasting the budget impact of a new treatment, 4 years of data must be presented: a 1-year baseline period and a 3-year forecast period in the base case. The base-case analysis must report costs by year. The total budget impact must be calculated based on the 3-year forecast period. Discounting should not be applied within the BIA.

Costs and Resource Use

The specific drug price(s) submitted for the lowest dispensable unit (to 4 decimal places) must be used in the sponsor's base case. The unit cost(s) must be stated transparently within the model. All submitted forms and strengths must be included in the submitted model.

Reporting

The technical report must incorporate a decision problem, methods, assumptions, and results that align with the submitted budget impact model.

Results must be presented individually, by drug program, before being aggregated to provide pan-Canadian results for the sponsor's base case and, if applicable, scenario analysis for any patient populations identified in the sponsor's requested reimbursement criteria.

The sponsor's base case and, if applicable, scenario analysis of the reimbursement-requested population, must be deterministic. Sensitivity analyses should be undertaken to assess parameter uncertainty on the base case and, if applicable, scenario analysis of the reimbursement-requested population.

All relevant comparators included in the submitted economic evaluation must be included in the BIA. In accordance with the economic evaluation, it may be determined that potentially relevant comparators were excluded from the pharmacoeconomic submission.

Specific considerations, such as those listed below, may apply depending on the submission:

- The method of dose preparation, dose stability, and specifics around potential drug wastage should be addressed within the BIA. Vial sharing, if applicable, may be considered in a scenario analysis.
- If there is a companion diagnostic test associated with the drug under review, the BIA (and model) must include a scenario analysis that captures the relevant costs for the companion tests in relation to the drug under review (e.g., test costs for all patients in whom the drug under review is considered, incorporating the impact of diagnostic accuracy of the test on the budget impact). The source(s) and assumption(s) of the relevant inputs should be provided as well.
- If the drug under review replaces an existing compounded product, a scenario analysis must be presented in which the compounded product is a comparator within the analysis.
- A scenario analysis must be presented that considers a broader Canadian health care payer perspective for the following technologies:
    - cell and gene therapies (e.g., consideration of costs to the health care system associated with the introduction and implementation of the new technology)
    - drugs that are partly or solely administered in hospital (e.g., consideration of drug costs borne by the hospital system)

- infusion therapy (e.g., consideration of the cost impact due to drug administration)
- If the full implementation is expected to extend beyond 3 years, a longer time horizon may be submitted as a scenario analysis.
- Change in market size (e.g., due to demographic change, changes in incidence, and so forth) should be considered if significant.

6.6.3.2. Budget Impact Model

An unlocked version of the budget impact model used to inform the technical report of the BIA must be provided.

The budget impact model must be programmed in Excel.

The model must be able to function in a stand-alone environment that does not require access to a web-based platform.

The sponsor must provide the model in its entirety, meaning CDA-AMC must have full access to the mathematical calculations and be able to fully execute the model based on modifications to parameters of interest. That is, calculations must not be done within the VBA code and CDA-AMC must be able to view within formulas how patients move through the model. CDA-AMC must be able to vary individual parameters, view the calculations, and run the model to generate results.

The BIA model must be flexible enough to be applied to the context of any individual drug program participating in the drug reimbursement review processes, which may differ with respect to the funding of comparators or the design of the program responsible for drug reimbursement. With the exception of drug prices (for which the same value should be used across all programs), input values used in the BIA should be specific to the individual drug program, where possible. When data specific to Prince Edward Island are unavailable, the inputs for Prince Edward Island are to be based on data from Nova Scotia.

The use of IFERROR statements modifies the output of a model file, masking errors and making it difficult to undertake a thorough appraisal of the model. IFERROR statements should not be used in the submitted budget impact model.

A breakdown of costs by perspective (i.e., drug program and, if applicable, health care payer) must be reported within the submitted budget impact model.

Results, by year, must be reported for both the reference and new drug scenario before the budget impact is calculated (as the difference between the new drug and reference scenario).

6.6.4. Supporting Material

Details regarding information used as input parameters in the pharmacoeconomic submission must be provided in detail. The sponsor must provide:

- A user guide for the economic model to ensure clarity on how to modify input parameters and how to run the economic model for the base case and all scenario analyses; within the user guide, please note the expected model run time.
- The full technical report of the indirect treatment comparison(s), if 1 or more indirect treatment comparison is used to inform model parameters in the submitted economic evaluation.
- Technical reports of any unpublished studies or analyses used to inform parameters or assumptions in either the pharmacoeconomic evaluation or BIA (this includes but is not limited to data from utility studies, patient registries, Clinical Study Reports, expert opinion, market research information, epidemiological data on disease incidence and/or prevalence); the technical report must be easily identified (i.e., provided separately to published studies or reports), and provide details of how input parameter values were derived, including a description of the study or dataset, the analysis plan, and results of the analyses; any modification or transformation of the results for use in the economic model must be described.
- Supporting documentation (i.e., references), numbered according to their respective number in the reference list, used to inform the methods, assumptions, and inputs in the economic evaluation and the BIA reports and models
- A RIS file with all references that are used in the pharmacoeconomic evaluation technical report and BIA technical report is required. The preferred format is a single RIS file, but separate RIS files for the pharmacoeconomic evaluation technical report and BIA technical report will be accepted.
- A document clarifying any key source(s) and assumption(s) of the relevant inputs for the companion diagnostic (e.g., articles, studies), if there is a companion diagnostic test associated with the drug under review.

Deviations from any of the requirements within the economic evaluation section must be discussed with and accepted in advance of filing the submission. Please submit the inquiry form with complete details of any proposed deviations from the requirements to the Pharmaceutical Submissions SharePoint Site. Alternative specifications may be considered in scenario analyses.

6.7. Reimbursement Status of Comparators

A completed template summarizing the reimbursement status of all appropriate comparators. The completed template must be filed as a Microsoft Word document.

6.8. Pricing and Distribution Information

6.8.1. Submitted Price

The submitted price for the drug, reported to 4 decimal places, as follows:

- price per smallest dispensable unit for all dosage forms and strengths available in Canada
- price for all packaging formats available in Canada.

The submitted price is the price per smallest dispensable unit that is submitted and that must not be exceeded for any of the drug programs following completion of the reimbursement review process. Only 1 price (anticipated or current market price) to 4 decimal places per smallest dispensable unit is to be submitted per drug that is to be reviewed (i.e., only 1 price for all indications undergoing review concurrently).

Confidential submitted prices are not accepted for applications filed for review through its reimbursement review processes. The submitted price is disclosed in all applicable reports. The price(s) of other treatments included in the pharmacoeconomic evaluation and in the BIA (e.g., comparators, concomitant medications) are not considered to be confidential and may be disclosed in the report.

The submitted price must be used in the pharmacoeconomic evaluation and in the BIA (budget impact reports and the models used to produce the results).

6.8.2. Method of Distribution

Indicate within the pricing and distribution document the method of distribution to pharmacies (e.g., wholesale, direct, or other arrangements).

6.9. Provisional Algorithm for Oncology Drugs

6.9.1. Proposed Place in Therapy Template

A completed proposed place in therapy template with the following information:

- the sponsor's proposed place in therapy for the drug under review, including a clearly stated rationale for the proposed place in therapy with supporting references (as required)
- an overview of the existing treatment algorithm for the indication of interest
- a proposed algorithm showing the place in therapy for the drug or regimen under review and the potential impact on the place in therapy of the currently reimbursed treatment options.

6.9.2. Studies for Studies Addressing the Sequencing of Therapies

Where applicable, a reference list and copies of published and unpublished studies that address the sequencing of therapies in relation to the drug under review, including the search strategy for those studies.

6.10. Companion Diagnostics

6.10.1. Clinical Validity and Utility of Companion Diagnostics

If applicable, provide a reference list and copies of articles that highlight the clinical validity and utility of the companion diagnostic(s) under review. In this context, clinical validity refers to evidence on diagnostic test accuracy, and clinical utility refers to evidence of improved health outcomes because of biomarker testing. If no references are provided, a statement will be required to confirm that a search has been undertaken but no references have been located.

6.10.2. Price of Companion Diagnostics

If applicable, the disclosable price for the companion diagnostic(s) be provided.

6.11. Additional Letter for Submissions Filed on a Pre-NOC Basis

Once the NOC or NOC/c has been issued, the sponsor must provide a signed letter, using the letter for sending the finalized indication template, indicating any wording changes to the Health Canada–approved final product monograph, as compared with the draft product monograph filed at the time of acceptance for review.

6.12. Additional Information Requests

To complete the review CDA-AMC may request additional information from the sponsor or Health Canada. Note the sponsor's continuing responsibility to advise CDA-AMC of any harms or safety issues that may arise during the time the submission is under review.

6.12.1. Economic Information

Throughout the review period, it may be found that the economic evaluation that has been filed by the sponsor contains limitations or that there is a lack of clarity in the pharmacoeconomic submission. In situations where there are important limitations with the economic evaluation (identified broadly as relating to model transparency, model validity, and exclusion of relevant comparators), the sponsor may be notified in writing of the limitations identified and provide a description of the specific issues. At this time, the sponsor will be given 5 business days to provide notification of which of the following options they would like to pursue:

- The sponsor plans to address the issues raised, in which case the review will be suspended in accordance with section 12.
- The sponsor will not be addressing the limitations raised, in which case the review will continue, and the limitations will be identified in the review report.
- The sponsor would like to voluntarily withdraw from the process.

- Failure to respond within 5 business or a request for an extension will result in the temporary suspension of the review in accordance with section 12.

If the sponsor plans to submit a revised economic model or budget impact model, the sponsor must submit a Log of Model Changes to CDA-AMC.

6.12.2. Health Canada Clinical Reviewer Report

CDA-AMC may request copies of all Health Canada clinical reviewer reports (Pharmaceutical Safety and Efficacy Assessment or Biologics Safety and Efficacy Assessment Report) pertaining to the evaluation of pivotal safety and efficacy clinical trials — including those associated with any previous negative decision received during any review iteration — for the indication to be reviewed. If the Pharmaceutical Safety and Efficacy Assessments or Biologics Safety and Efficacy Assessment Reports are unavailable from Health Canada at the time the request is received, the sponsor should provide the reports as soon as they are available (i.e., on the day of, or the business day after, receipt from Health Canada).

6.12.3. Health Canada Clarifaxes and Clarimails

Copies of Clarifaxes and Clarimails and/or responses to Clarifaxes and Clarimails issued by the sponsor may be requested. These documents must be provided in searchable format (i.e., PDF or .docx).

6.12.4. Clinical Study Reports and Periodic Safety Update Reports

Complete copies or sections of Clinical Study Reports and Periodic Safety Update Reports from the sponsor may be requested. These documents must be provided in searchable format (i.e., PDF or .docx).

7. Engagement With Interested Parties

CDA-AMC follows strict processes to evaluate evidence independently and objectively. It is inappropriate and unhelpful to the process for the sponsor, individual patients, patient groups, consumer advocacy groups, individual clinicians, professional organizations, or lobbyists to directly contact expert committee members with regards to a specific drug review.

7.1. Sponsor Engagement

7.1.1. Communications Between CDA-AMC and the Sponsor

Once an application for a reimbursement review has been filed, CDA-AMC will only address procedure and process-related matters with sponsors via email, unless otherwise defined in this document (e.g., a conference call offered during the reconsideration process). Due to the volume of requests and the need to optimize limited resources, CDA-AMC is unable to offer conference calls to sponsors that have

questions regarding the process and encourages sponsors that have questions regarding the process to submit a written inquiry. A written response will be provided in a timely manner. In-person meetings will not be offered.

Direct contact between a sponsor and expert committee members (in their capacity as members of the expert committees) or the review team is not permitted during the review process. Direct approaches in any form to committee members or the review team may be viewed as introducing conflict of interest and may create an appearance of bias or unfairness. Direct contact by a sponsor with 1 or more members of the review team may result in a significant delay in the review process because additional steps may be required to obtain an unbiased recommendation on the product.

Consultants working on behalf of a sponsor are required to copy an official contact for the sponsor on all email correspondence with CDA-AMC. CDA-AMC will not respond to any email correspondence from a consultant if an official contact for the sponsor has not been copied.

7.1.2. Commentary and Feedback

Sponsors are provided with the opportunity to review and comment on the draft report (i.e., clinical report, pharmacoeconomic report, and ethics report, as applicable) prior to deliberation by the expert committee. CDA-AMC will provide responses to the commentary and revise the report as required. Sponsors will be provided with the responses 8 business days prior to the scheduled expert review committee meeting. Refer to section 10 for details on the process for the sponsor review of the draft report. Sponsors will have the opportunity to review and provide feedback on the draft recommendation (section 11.4.2), as well as to file a request for reconsideration (refer to section 11.5).

7.1.3. Meetings with CDA-AMC

7.1.3.1. Presubmission Meetings

Purpose

Presubmission meetings are offered to facilitate the efficient preparation and filing of applications. The presubmission meeting provides the opportunity for CDA-AMC staff and the sponsor to discuss the pending application. These meetings are offered on a case-by-case basis to discuss and resolve procedural questions regarding the pending application. This may include:

- clarification of application requirements
- assignment of review complexity
- proposed deviations from the required project scope
- acceptability of proposed deviations from the pharmacoeconomic requirements
- splitting applications into multiple review projects.

These meetings would occur prior to the application being filed and would be arranged only when required (i.e., the sponsor is seeking guidance, and we require dialogue to reach a decision on the issue).

Timing

Once an application has been filed, it is no longer eligible for a presubmission meeting. Sponsors may request a pre-submission meeting for an application to be filed within 12 months of the meeting. To ensure maximum value from the discussion, sponsors are encouraged to schedule the presubmission meeting at least 20 business days prior to the anticipated date the application will be filed.

Scheduling

Only one presubmission meeting will be permitted for each pending application. The sponsor will request the meeting using an online portal. CDA-AMC will evaluate the request and determine if a meeting is appropriate and will notify the sponsor as soon as possible (typically within 5 business days). If the meeting is necessary, CDA-AMC will schedule the time of the meeting. Please note that pre-submission meetings will only be offered when discussion is required to resolve the questions submitted by the sponsor (i.e., we anticipate the majority of pre-submission inquiries will continue to be managed through the submission of standardized application forms and correspondence from CDA-AMC).

Meeting Package

Sponsors are required to submit the following information to CDA-AMC no later than 5 business days prior to the target date of the meeting:

- proposed agenda
- list of sponsor attendees
- questions for discussion with CDA-AMC
- slide presentation (if applicable).

Meeting Logistics and Format

Presubmission meetings are intended to be decision-oriented with formal follow-up confirming the decisions reached on each of the issues discussed. These meetings are 30 to 45 minutes depending on the number of items for discussion. Presubmission meetings are held exclusively via web conference (in-person meetings will not be offered).

Attendance

As the focus of these meetings is on clarification of procedural questions. Attendance will typically be limited to CDA-AMC staff and the sponsor (with consultants as required). These meetings are not open to patient groups. The sponsor may invite a clinical specialist if their attendance and input is required to help facilitate timely resolution to the inquiry (please notify CDA-AMC in advance of the meeting).

Post-Meeting Requirements

The sponsor will be required to send a written summary of the key discussion points to CDA-AMC within 3 business days of the meeting. This will ensure that there is a common understanding between CDA-AMC and the sponsor regarding the issues discussed during the presubmission meeting.

7.1.3.2. Evidence Presentation Meeting

Purpose

The evidence presentation meeting is an opportunity for the sponsor to present and discuss the clinical and economic evidence. These meetings are held shortly after the application has been received by CDA-AMC. This approach offers several important advantages: attendance is optimized as all participants will be directly involved in the project and the time with the invited clinical experts will be maximized to focus exclusively on the evidence and place in therapy (i.e., procedural matters will now be managed in the presubmission meeting). CDA-AMC staff may pose questions throughout the discussion. As the review will only be in the initiation phase, the review team will not be in a position to address questions from the sponsor regarding the review.

Timing

The evidence presentation meeting must occur within a timeframe of approximately 15 business days (between day 5 and day 20 after the application has been filed).

Scheduling

The sponsor must request an evidence presentation meeting and provide tentative dates within the advance notification form. The sponsor must provide tentative dates within the range of 5 to 20 business days after the application will be filed with CDA-AMC (exceptions will not be granted). The evidence presentation will not be scheduled later than 20 business days after the application has been filed for review.

Meeting Package

Sponsors will be required to complete a briefing paper template prior to the meeting. The purpose of the briefing paper is to provide the information required to adequately prepare for the meeting. The completed document must not exceed 10 pages. The completed template along with a draft version of the presubmission meeting slides (in .pptx form) must be uploaded to the Pharmaceutical Submissions SharePoint site in the “Evidence Presentation Meeting” folder. The briefing paper and slides must be filed no later than 10 business days prior to the scheduled date of the meeting, with the final slides submitted 3 business days in advance. Failure to provide these documents within this time frame may result in postponement or cancellation of the meeting. The presentation must not include new information that has not been submitted to CDA-AMC in the application.

Meeting Logistics and Format

CDA-AMC will open the meeting by welcoming participants. The sponsor will present the evidence, including the clinical and economic information. CDA-AMC may pose questions throughout the presentation (please note that questions will not be sent to the sponsor in advance of the meeting). To ensure that the meeting is conducted efficiently, it is recommended that the sponsor appoint one of its team members to chair the meeting. This helps ensure that the sponsor can address all the key items within the allotted time frame.

The following items are out of scope for the evidence presentation meetings: CDA-AMC interpretation of the evidence; CDA-AMC appraisal of the evidence; and direction or speculation regarding the expert committee recommendation. As the CDA-AMC review will only be in the initiation phase, the review team will not be in a position to address questions from the sponsor regarding the review, including commentary on the evidence that will be included in the clinical review or the outcomes that will be assessed using the GRADE methodology.

One member of the sponsor's team will be responsible for sharing the slide deck and advancing the slides throughout the meeting. The sponsor is responsible for ensuring a member of the team is familiar with Microsoft Teams ahead of time and can share their screen to present the slide deck. It is strongly recommended that the sponsor designate another team member as a "backup" presenter in case of any technical difficulties. Meetings will be recorded for internal purposes. The recordings are not distributed outside of CDA-AMC.

Sponsors must note that the meeting materials are not necessarily shared with members of the committee. All the information presented in the meeting must be included within the application documents (i.e., no new information should be shared during the evidence presentation meeting).

Attendance

CDA-AMC representation will include the review managers and other delegates as required. Only the names of the review manager(s) will be disclosed to the sponsor during the meeting (i.e., other members of the review team will participate anonymously).

Sponsors may bring consultants and/or clinical experts as representatives. It is recommended that a relevant Canadian health care professional participate in the evidence presentation meeting. For example, a clinical specialist who has expertise on the disease and the available treatments in Canada, particularly in the case of an unmet medical need.

These meetings are not open to patient group representatives. Patients' perspectives, experiences and values are integrated formally into the reimbursement review processes through the patient group input procedure as well as lived experience presentations at expert committee meetings for a subset of complex reviews. Patient groups are welcome contact our patient engagement team if they have questions regarding the process.

Representatives from the participating drug programs, pCPA, Canadian Blood Services, Canadian Association of Provincial Cancer Agencies (CAPCA), and INESSS may attend these meetings at their discretion.

Post-Meeting Requirements

Potential action items from these meetings will be identified on a case-by-case basis and would generally fall within the scope of the current processes for requests for additional information from the sponsor.

7.1.3.3. In-Review Meeting

Purpose

The objective of the in-review meetings will be to provide an opportunity for CDA-AMC and the sponsor to resolve submission-related issues that arise during the review in a timely manner.

Acceptable meeting topics should focus on issues related to:

- clarifications regarding interpretation and application of CDA-AMC procedures in response to issues that arise during a review (e.g., revised regulatory timelines, sponsor has new information regarding the product)
- clarification of the patient populations identified by the approved or anticipated indication
- discussion on the impact of revisions to the approved dosage regimens (i.e., differences between the information in the draft and final product monographs)
- lack of agreement between CDA-AMC and the sponsor regarding the inclusion of other evidence in the review
- important limitations identified with the sponsor's economic evaluation (e.g., issues that may preclude the generation of a CDA-AMC base case)
- temporary suspensions due to incomplete information and/or delays with the regulatory review timeline.

The following topics will not be discussed during in-review meetings:

- CDA-AMC interpretation of the evidence
- CDA-AMC appraisal of the evidence
- direction or speculation regarding the expert committee recommendation
- questions related to the threshold used for issuing guidance on price reduction scenarios
- questions related to parametric functions used for extrapolation
- questions related to scientific methods used to derive the CDA-AMC base case.

Timing

Sponsors would be offered a maximum of 1 meeting anytime between acceptance for review and the issuance of the draft recommendation.

Scheduling

Only one in-review meeting will be permitted for each application under review. The sponsor will request the meeting by contacting formulary-support@cda-amc.ca. CDA-AMC will evaluate the request and determine if a meeting is appropriate and will notify the sponsor as soon as possible (typically within 5 business days). If the meeting is necessary, CDA-AMC will schedule the time of the meeting. These meetings will typically be requested by the sponsor. In select cases, CDA-AMC may contact the sponsor requesting a meeting.

Meeting Package

The sponsor will be required to submit a proposed agenda including the time allotted per question and the names of the two people who will represent the sponsor. The agenda must be received no later than 3 business days prior to the meeting to allow CDA-AMC to optimize attendance at the meeting.

Meeting Logistics and Format

The meetings will be a maximum of 45 minutes. The meeting may be recorded by CDA-AMC for internal purposes.

Attendance

The sponsor will be limited to two attendees (typically one person familiar with the economic evaluation and one familiar with the clinical evidence). Attendees for CDA-AMC will be determined based on the objective of the meeting.

Post-meeting Requirements

The sponsor will be required to send a written summary of the key discussion points to CDA-AMC within 3 business days of the meeting. This will ensure that there is a common understanding between CDA-AMC and the sponsor regarding the issues discussed during the midpoint meeting.

7.1.3.4. Reconsideration Meeting

Purpose

The reconsideration meeting provides the sponsor with an opportunity to elaborate on the issues that were raised in their request for reconsideration that was filed. These meetings are not offered for a situation where the request for reconsideration has been filed by the participating drug programs. In such cases, CDA-AMC provides the complete written request for reconsideration to the sponsor and provides

an opportunity for direct input and commentary on the request. CDA-AMC cannot facilitate a meeting between the sponsor and representatives of the public drug programs.

Scheduling

The sponsor will request the meeting using the reconsideration template.

Meeting Package

If providing a presentation, the sponsor must limit the number of slides to 30 or less.

Meeting Logistics and Agenda

Reconsideration meetings are only offered via web conference and can be a maximum of 1 hour. In-person meetings are not offered for reconsideration meetings. CDA-AMC will provide the meeting information prior to the meeting and may record the call for internal purposes.

CDA-AMC will open the meeting by welcoming participants and stating the purpose of the reconsideration meeting. The remaining content of the meeting and the presenters are at the discretion of the sponsor. To ensure that the meeting is conducted efficiently, CDA-AMC recommends that the sponsor appoint one of its team members to chair the call. This helps ensure that the sponsor can address all of the key items within the allotted time frame. CDA-AMC may pose questions throughout the presentation to help ensure that the issues being raised by the sponsor are clearly understood.

Attendance

The sponsor is free to select its attendees; however, it is recommended that sponsors ensure that at least one person on the call is familiar with the clinical and economic details of the drug under review, including the appraisal, interpretation, and reanalyses reported in the review report and the draft recommendation. Sponsors are welcome to invite clinicians and/or patients to participate in the web conference, provided they have agreed to maintain the confidentiality of the proceedings, including any CDA-AMC documents that have not been posted publicly. Attendance will be capped at a maximum of 1 clinician and/or 1 patient representative at each meeting.

Key CDA-AMC staff will attend the meeting (e.g., program directors and review team members). The names of the review team members are not disclosed to the sponsor, except for the review manager(s). CDA-AMC will extend an invitation to observe the reconsideration meeting to members of the Formulary Working Group or Provincial Advisory Group (as applicable); however, their attendance for these meetings will be optional. At the sponsor's request, CDA-AMC may extend an invitation to INESSS to observe the reconsideration meeting. In these situations, CDA-AMC will extend the invitation to INESSS; however, their participation is optional. Sponsors must communicate if they would like INESSS to be invited to the meeting in section 1 of the reconsideration request template.

Post-Meeting Requirements

The sponsor is required to prepare a draft summary of the discussion using the template provided by CDA-AMC. The summary must not exceed 2 pages and must be submitted to CDA-AMC in accordance with the deadlines provided at the meeting. Delays in providing the summary could impact the target expert committee meeting. CDA-AMC staff will review and finalize the summary (revising as required to ensure clarity). Expert committee members will be provided with the meeting materials and the summary of the meeting.

7.1.3.5. Post-Recommendation Meeting

Purpose

These meetings are intended to discuss procedural matters and are not intended to discuss the evidence submitted by the sponsor or the conclusions from the expert committee meeting. A representative from our Scientific Advice program may attend the meeting to discuss opportunities for advice on developing evidence to support a resubmission to CDA-AMC.

Timing

These meetings will only be offered after the final recommendation has been published on the CDA-AMC website.

Scheduling

Only one post-recommendation meeting will be permitted for each recommendation. The sponsor will request the meeting by contacting formulary-support@cda-amc.ca. CDA-AMC will evaluate the request and determine if a meeting is appropriate and will notify the sponsor as soon as possible (typically within 5 business days). If necessary, CDA-AMC will schedule the time of the meeting.

Meeting Package

The sponsor will be required to submit a proposed agenda including the time allotted per question and the names of the two people who will represent the sponsor. The agenda must be received no later than 5 business days prior to the meeting to allow CDA-AMC to review the materials and optimize attendance at the meeting.

Meeting Logistics and Format

CDA-AMC will open the meeting CDA-AMC will open the meeting by welcoming participants and stating the purpose of the meeting. The remaining content of the meeting will be determined based on the nature of the questions posed by the sponsor.

Table 9: Opportunities for Meetings With CDA-AMC and Industry

Time frame	Duration	Objective	Eligibility	Attendance
Presubmission meeting				
Any time within 12 months of the target date of filing the application	30 to 45 minutes	Opportunity to address questions concerning: • procedures • application requirements • application scope • review complexity • requests for deviation • content of clinical submission template	Case-by-case allowance depending on the nature of the question (e.g., does it require dialogue or would an email or letter be sufficient)	CDA-AMC advisors for methods, procedures, and process Sponsor contacts and consultants (as required)
Evidence presentation meeting				
Within 5 to 20 business days after filing the application	45 minutes	Opportunity for sponsor to present key clinical and economic evidence Opportunity for sponsor to address questions concerning: • proposed place in therapy • clinical and pharmacoeconomic evidence • diagnostic and other testing requirements • implementation considerations	Offered for all standard and complex reviews Not offered for tailored reviews	CDA-AMC review team Public drug programs (optional) Sponsor contacts and consultants (as required) Sponsor-invited clinical experts
In-review meeting				
Maximum of 1 meeting any time between acceptance for review and issuance of the draft recommendation	30 minutes	Opportunity to resolve submission-related issues that arise during the review in a timely manner	• Clarifications regarding procedures • Clarification of target population(s) • Impact of revised dosages	• Attendees for CDA-AMC will be determined based on the objective of the meeting • Sponsor contacts and consultants (as required)

Time frame	Duration	Objective	Eligibility	Attendance
			• Lack of agreement regarding inclusion of other evidence • Issues that preclude a CDA-AMC base case • Suspensions	
Reconsideration meeting				
Within 20 business days of accepting the reconsideration request	1 hour	Opportunity to elaborate on the issues that were raised in the request for reconsideration	• Requests for reconsideration from the sponsor • Not offered for jurisdictional requests for reconsideration	• CDA-AMC review managers • Sponsor contacts and consultants (as required) • Sponsor-invited clinical experts
Post-recommendation meeting				
Within 2 months of the final recommendation being posted on the CDA-AMC website	30 minutes	Opportunity to discuss and elaborate on the rationale and potential future avenues for resubmissions or reassessments for a do not reimburse recommendation or for reimbursement conditions	Case-by-case assessment depending on the complexity of the sponsor's questions	• Attendees for CDA-AMC will be determined based on the objective of the meeting. • Sponsor contacts and consultants (as required)

CDA-AMC = Canada's Drug Agency.

7.1.3.6. Pipeline Meetings

Purpose

Pipeline meetings will provide an opportunity for industry to present an overview of their forthcoming pharmaceutical and diagnostic products and pose questions on procedural and process initiatives. Pipeline meetings are intended to be mutually beneficial for industry and CDA-AMC; sponsors will benefit through early advice on questions regarding the preparation of their applications and CDA-AMC will benefit through earlier notification and dialogue on new treatments.

Sponsors are encouraged to discuss emerging therapies that may pose implementation challenges and require co-ordination across the broader health care system to facilitate integration into Canadian practice. This includes novel diagnostic and associated testing procedures or situations where existing

testing resources could be substantially impacted. Early identification of these potential issues could allow CDA-AMC to initiate work on implementation guidance earlier in the product life cycle to help facilitate overall health system readiness.

Frequency of Pipeline Meetings

To ensure fair access, sponsors will typically be limited to 1 pipeline meeting per 2-year period. Although the preference would be for a combined meeting, sponsors may request separate meetings for cancer and non-cancer therapeutics, if required (e.g., insufficient time due to a high volume of products in both areas).

Requesting a Pipeline Meeting

Sponsors must register with the Pharmaceutical Submissions SharePoint site before filing a request for a pipeline meeting. For detailed information on how to register, please consult Pharmaceutical Submissions SharePoint Site – Setup Guide. When registering for the SharePoint site, sponsors should indicate “pipeline meeting” in the reason for requesting access section of the form. Once access to the site has been given, sponsors are required to complete a presubmission meeting request form and upload it to the assigned secure area of the Pharmaceutical Submissions SharePoint site.

Briefing Paper and Meeting Materials

Sponsors are required to complete a pipeline meeting briefing paper template for all pipeline meetings. The purpose of the briefing paper is to provide the information required to adequately prepare for the meeting. The briefing paper is intended to provide a concise summary of key issues and questions. The completed document must not exceed 12 pages. The completed template along with a draft version of the meeting slides (in .ppt form) must be uploaded to the Pharmaceutical Submissions SharePoint site in the Pipeline Meeting folder. The briefing paper and slides must be filed no later than 10 business days before the scheduled date of the meeting. Failure to provide these documents within this time frame may result in the meeting being postponed.

Attendees

Given the purpose and scope of pipeline meetings, attendees will be limited to the sponsor and CDA-AMC. Representatives from INESSS, the drug programs, and the pCPA may attend pipeline meetings.

Meeting Logistics and Agenda

Pipeline meetings are scheduled for a maximum of 1.5 hours and will be held via Microsoft Teams. CDA-AMC will schedule the meeting and provide the sponsor with meeting details.

CDA-AMC will open the meeting by welcoming participants. The remaining content of the meeting and the presenters are at the discretion of the sponsor. To ensure that the meeting is conducted efficiently, we recommend that the sponsor appoint 1 of its team members to chair the meeting. This helps ensure that the sponsor can address all the key items within the allotted time frame. CDA-AMC may pose

questions throughout the presentation to help ensure that the issues being raised by the sponsor are clearly understood.

A member of the sponsor's team will be responsible for sharing the slide deck and advancing the slides throughout the meeting. The draft slides must be submitted via the assigned secure area on the Pharmaceutical Submissions SharePoint site 10 business days in advance of the meeting, with the final slides submitted 1 business day in advance of the meeting. This allows the CDA-AMC team sufficient time to review the slides and prepare accordingly.

The sponsor is responsible for ensuring a member of the team is familiar with Microsoft Teams ahead of time and can share their screen to present the slide deck. It is strongly recommended that the sponsor designate another team member as a "backup" presenter in case of any technical difficulties.

Pipeline meetings will be recorded for internal purposes. The recordings are not distributed.

7.2. Patient Engagement

7.2.1. Role of Patient Groups

Patient group input provides patients' experiences and perspectives of living with a medical condition for which a drug under review is indicated, their experiences with currently available treatments, and their expectations for the drug under review. This information is used in all phases of the review, including appraisal and interpretation of the evidence, and the development of recommendations. Table 10 provides a summary of the key milestones for patient group involvement in the reimbursement review processes.

Table 10: Key Milestones for Patient Group Engagement

Milestones	Description
Call for patient group input	The call for patient input is issued 29 business days before the anticipated date of filing the application and will be open for 35 business days from the date the call for input is issued in the weekly update.
Posting complete patient group input[a]	All patient group input will be posted on the website (this typically occurs approximately 2 weeks after call for input closes).
Commentary on recommendations	Patient groups will have 10 business days to review and comment on the draft recommendations during the feedback period.

[a] This will include all conflict-of-interest declarations.

7.2.2. Patient Group Input and Feedback

7.2.2.1. Call for Patient Input

The call for patient input regarding a submission, resubmission, or standard reassessment is posted 29 business days in advance of the anticipated filing date (as provided in the advance notification form) or

on the same day a request for advice is received. Patient groups have a total of 35 business days (from the date the call for input is issued in the weekly update) for preparing and submitting their input.

Open calls for patient input are available via:

- Website (as a pending drug submission and an open call for patient input).
- Weekly Summary newsletter that summarizes all notifications and is sent to subscribers every Thursday.
- Social media platforms including X (@CDA_AMC) and Facebook (@CDA.AMC).

If a pending submission, resubmission, or standard reassessment is delayed following the issuance of the call for patient input, the call may be re-posted if the delay is 6 months or longer. This is undertaken for 2 reasons:

- to ensure that the patient group input reflects the current perspective from the patient group(s)
- to provide an opportunity for any additional groups to contribute to the reimbursement review process.

7.2.2.2. Submitting Patient Input

Patient input is submitted by patient groups. Individual patients or caregivers who wish to provide input are encouraged to work with a patient group that represents their condition to prepare a group submission. Patient input from individual patients and caregivers will only be accepted when there is no patient advocacy group representing patients with a condition for which a drug under review is indicated. Individual patients and caregivers who wish to submit input for a drug review should first contact CDA-AMC to confirm the absence of a relevant patient group. Upon confirmation that no relevant patient group exists, interested individuals will be provided with the individual patient and caregiver template for completion. The process for providing input, and how the input is used and posted, remains the same as that for patient groups, with minor modifications, as applicable, for an individual patient or caregiver.

Patient groups are asked to use the patient input template that is posted on the website. This template has questions and prompts to help guide patients to provide the information that will be most helpful to the review team and the expert committees.

Patient groups must submit their input as a Microsoft Word document by the posted deadline for the information to be used in the reimbursement review process.

7.2.2.3. How Patient Group Input Is Used

All patient group input received for the drug under review is collated. The complete patient group input is posted and included in the committee briefing materials. The patient members on the expert committees present the patient input at the deliberations, and a summary of the patient input discussion is included in the recommendation documents. A summary of input is also included in the report.

All patient input submissions are kept on file and may be referred to in future reviews of the same drug or other drugs with similar indications.

7.2.2.4. Posting Patient Group Input

The patient group submissions for each drug are consolidated for posting on the website. Posting typically occurs approximately 2 weeks after the call for input closes. The conflict of interest information will be included in the posted material. CDA-AMC takes reasonable precautions to remove any private information, such as names of individual patients, before posting the patient group input submissions in their entirety. However, it is the responsibility of the patient group to ensure that no private information is included in the submissions.

7.2.2.5. Feedback on Draft Recommendations

All draft recommendations are posted on the website for feedback. The feedback period begins when the draft recommendation is posted on the CDA-AMC website. Patient groups and other interested parties will have 10 business days to review the draft recommendation and provide feedback using the template. Refer to section 11.4.2 for complete details on the procedures for feedback on draft recommendations.

7.2.3. Person With Lived Experience

For complex reviews meeting the criteria for scenarios 1 and 2, CDA-AMC will seek to engage a person with experience with the condition under review. (i.e., a patient, caregiver, close support, or family member) The person with lived experience (PWLE) participates in the expert committee meeting by delivering a brief presentation and answering questions from the committee members. The goal of including lived experience presentations at committee meetings is to supplement the written patient group input by providing an opportunity for committee members to hear firsthand about the real-world challenges, needs, and impacts of the condition under review (and its treatment) on patients and caregivers, and gain insights into the social, ethical, and practical implications of treatments.

Patient group Input and PWLE presentations serve important but distinct roles. Patient group input helps ensure that committee members have a well-rounded understanding of collective patient needs and priorities at a system level, while PWLE presentations provide a more detailed and personal perspective that can add depth to the committee's understanding of a condition and allows an opportunity to obtain further insights directly from a PWLE during the Question & Answer period.

7.2.3.1. Process Overview

Outreach and Recruitment

CDA-AMC will seek to engage a PWLE in collaboration with a patient group, clinician group, or community-based group or clinic. CDA-AMC staff will identify outreach targets based on:

- Reviewing past input and feedback submissions in related therapeutic areas for relevant patient groups, clinician groups, or community-based groups
- Utilizing CDA-AMC contacts.
- Researching patient groups and organizations online.

Additionally, patient groups and clinician groups are invited to contact CDA-AMC to express an interest in participating in this process by contacting PCIEngagement@cda-amc.ca.

Interested parties will be provided with written information that outlines the product, condition and indication of the reimbursement review and the role and responsibility of the PWLE within this engagement. The Engagement Details document also includes the level of commitment involved, timelines of participation, estimated effort required, documentation required, as well as contact information for the assigned CDA-AMC engagement officer for the review.

When seeking a PWLE to present at the expert committee meeting for a reimbursement review, preference will be given to people with experience that matches the indication under review. If such a person cannot be engaged, a person with experience that is closely related to the indication under review (e.g., experience with the same disease but at a different stage) may be considered. In instances where there are multiple individuals interested in participating, CDA-AMC will prioritize the inclusion of underrepresented and underserved populations in our selection process to ensure diverse perspectives and equitable representation.

CDA-AMC will endeavor to engage a person with relevant lived experience to present for every complex review meeting the criteria for applying this process, but this may not always be possible. If a PWLE is not found for the review or if they are not able to attend due to unforeseen circumstances, the committee meeting will proceed as scheduled (i.e., the application will not be deferred to a subsequent committee meeting) and the expert committee will be informed of the efforts made to find a PWLE, and the circumstances around being unable to do so. CDA-AMC will endeavor to accommodate the participant's needs to ensure meaningful participation.

Preparation

Once a PWLE has been identified, CDA-AMC staff will offer a preparatory meeting to support and provide guidance leading up to the presentation at the committee meeting and following the meeting. The PWLE will be provided with a brief introduction to the reimbursement review process and their role within the process. The PWLE will be asked to complete a conflict-of-interest declaration and consent form with compliance with CDA-AMC Conflict of Interest Policy confirmed prior to participating in the committee meeting. The PWLE is provided with guiding questions to help them develop and frame their presentation in a manner aligned with the deliberative framework, as well as additional details on the reimbursement review and committee meeting processes. An Engagement Officer is available to provide feedback and support to the presenter leading to the committee meeting.

Committee Meeting

The PWLE delivers their presentation at the committee meeting and responds to questions from the committee members, facilitated by CDA-AMC staff. Typically, a presentation by a PWLE will include a brief personal introduction, followed by a narrative of the individual's treatment journey, focusing on:

- Treatment outcomes and goals that are important to them
- Impacts of the disease and its treatment on daily life & well-being, including emotional and social aspects
- Experiences with treatments for the disease
- Challenges with accessing and using treatment
- Social, ethical, and financial considerations relevant to treatment access and use.

Additionally, they are invited to share other key aspects about their condition or treatments that are important to them for consideration for committee members. Representatives from patient groups involved in the process of engaging with a PWLE are invited to attend, observe, and act as support for the PWLE during their presentation. Once the presentation is complete, the PWLE and patient group representatives are asked to leave the meeting prior to the in-camera portion of the meeting.

Closing the Loop

Following the presentation, the PWLE is offered an optional meeting to debrief with a CDA-AMC Engagement Officer at their convenience. A summary of the lived experience presentation will be reflected in the recommendation after verification by the PWLE, to ensure it is appropriately summarized. Additionally, they can be thanked by name in the recommendation or remain anonymous according to their preference. Participants are kept informed of the outcome of the reimbursement review and provided an honorarium as a gesture of appreciation for their contributions to the review.

7.3. Clinician Engagement

7.3.1. Clinician Group Input and Feedback

7.3.1.1. Role of Clinician Groups

Clinician group input is used in all phases of the review, including appraisal of evidence, and interpretation of the results. The clinician group input submissions are posted on the website and included in committee briefing materials. A summary of the clinician input is included in the recommendation documents. A summary of input is also included in the report. Table 11 provides a summary of the key milestones for clinician group involvement in the reimbursement review processes.

Table 11: Key Milestones for Clinician Group Engagement

Milestones	Description
Call for clinician group input	The call for clinician group input is issued 29 business days before the anticipated date of filing the application and will be open for 35 business days from the date the call for input is issued in the weekly update.
Posting complete clinician group input[a]	All clinician group input will be posted on the website (this typically occurs approximately 2 weeks after call for input closes).
Commentary on recommendations	Clinician groups will have 10 business days to review and comment on the draft recommendations during the feedback period.

[a] This will include all conflict-of-interest declarations

7.3.1.2. Call for Clinician Input

The call for clinician input regarding a submission, resubmission, or standard reassessment is posted 29 business days in advance of the anticipated filing date (as provided in the advance notification form) or on the same day a request for advice is received. Groups or associations of health care professionals will have a total of 35 business days (from the date the call for input is issued in the weekly update) for preparing and submitting their input.

Open calls for clinician input are available via:

- Website (as a pending drug submission and an open call for patient input).
- Weekly Summary newsletter that summarizes all notifications and is sent to subscribers every Thursday.
- social media platforms including X (@CDA_AMC) and Facebook (@CDA.AMC).

If an application is delayed following the issuance of the call for clinician input, the call for input may be re-posted if the delay is 6 months or longer. This is undertaken for 2 reasons:

- to ensure that the clinician input reflects the current perspective from the group(s) or association(s)
- to provide an opportunity for any additional groups to contribute to the reimbursement review process.

7.3.1.3. Submitting Clinician Group Input

Input from clinicians is submitted by groups or associations of health care professionals. Individual clinicians who wish to provide input are encouraged to work with a group that represents their profession to prepare a group submission. Input from individual clinicians will only be accepted when there is no relevant group or association that could provide input for the drug under review. Individuals who wish to submit input for a drug review should first contact CDA-AMC to confirm the absence of a relevant group or association.

Clinicians providing input on behalf of a group or association are asked to use the clinician input template that is posted on the website. This template has questions and prompts to help guide respondents to provide the information that will be most helpful to the review team and the expert committees in their work. CDA-AMC maintains the discretion to remove any information that may be out of scope for the review or not within the intent of the clinician input template. The input must be filed as a Microsoft Word document by the posted deadline date for the information to be used in the reimbursement review process.

7.3.1.4. Posting Clinician Group Input

The information will be posted for the drug under review after the call for clinician input is closed. The clinician group submissions for each drug are consolidated for posting on the website. Posting typically occurs approximately 2 weeks after the call for input closes. The conflict-of-interest information will be included in the posted material.

7.3.1.5. Feedback on Draft Recommendations

All draft recommendations are posted on the website for feedback. The feedback period begins when the draft recommendation is posted on the website. Clinician groups and other interested parties will have 10 business days to review the draft recommendation and provide feedback using the template. Refer to section 11.4.2 for complete details on the procedures for feedback on draft recommendations.

7.3.2. Clinical Experts on the Review Team

7.3.2.1. Role of Clinical Experts

All reimbursement review teams include at least 1 clinical specialist with expertise in the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). In addition, the clinical experts are invited to attend expert committee meetings to address any issues raised by the committee.

Standard and tailored reviews will typically include 1 to 2 clinical specialists as part of the review team while complex reviews will typically include 3 or more clinical specialists as part of the review team.

Table 12: Key Functions of Clinical Experts

Phase	Role in the reimbursement review process
Review phase	• Assisting in the critical appraisal of clinical evidence • Interpreting the clinical relevance of the results • Providing guidance on the potential place in therapy • Reviewing and advising on the appraisal and interpretation sections of the clinical report • Advising on the assumptions used in the pharmacoeconomic analysis to assist in critical appraisal and to inform reanalyses • Advising on implementation issues raised by jurisdictions
Recommendation phase	• Attending expert committee meetings to address any issues raised by the committee • Providing input on requests for reconsideration
Implementation phase	• As part of an implementation advice panel, experts may advise on outstanding implementation issues and further develop and refine reimbursement conditions • Advising on treatment sequencing within a particular indication for oncology drugs

7.3.2.2. Clinical Panels

In addition to engaging clinical specialists as part of the review team, clinical panels may be established for complex reviews that meet the criteria for scenarios 1, 2, 3, and 4. Requests from the drug programs to initiate a clinical panel for other reviews will also be considered. Such considerations could be based on the perceived complexity of the drug from an implementation perspective.

These panels will be used to characterize unmet therapeutic needs, assist in identifying and communicating situations where there are gaps in the evidence that could be addressed through the collection of additional data, promote the early identification of potential implementation challenges, gain further insight into the clinical management of patients living with a condition, and explore the drug's potential place in therapy (e.g., potential reimbursement conditions).

The panels will comprise clinical experts with experience in the diagnosis and management of the condition for which the drug under review is indicated. Potential experts will be identified by CDA-AMC, and whenever possible, representation from across Canada will be sought. The number of clinical specialists included on the panels may vary based on input from the drug programs and the complexity of the review. The identities of the clinical experts who participate in the panels will remain confidential.

The attendance at clinical panel meetings will be limited to the clinical experts, key expert committee members (i.e., chairs and lead presenters), and CDA-AMC staff (i.e., review team members). The inclusion of a clinical panel in the review process will have no impact on the overall review timelines. The sponsor will be notified that the review will include a clinical panel at the time the application is accepted for review.

7.3.2.3. Input From Clinical Experts

CDA-AMC engages with the clinical experts (with or without a supplemental clinical panel) before the expert committee meeting to ensure that the committee has this information available to inform their deliberation and recommendation. The input from the clinical experts will be made available to the sponsor for review and commentary before the expert committee meeting. CDA-AMC will aim to integrate the input of the clinical experts into the review report before it is sent to the sponsor for review and commentary.

The report will still be sent to the sponsor for comment in the event CDA-AMC is unable to integrate the input from the clinical experts into the draft review report at the time the distribution is scheduled to occur (e.g., due to challenges scheduling meetings with the clinical experts). In the event this occurs, the sponsor will receive the clinical expert input for review and commentary in a separate distribution as soon as possible. The sponsor will be notified if there are any anticipated delays regarding these steps in the process.

Any feedback from the sponsor regarding the input from the clinical experts will be reviewed and addressed and the experts (as required). If deemed appropriate, the review report will be revised. The input from the clinical experts will be made available to the expert committee for their deliberations on the drug under review.

7.3.2.4. Clinical Experts Interested in Participating

Clinical experts who are interested in participating in the reimbursement review process can register by completing a web form with contact information and details about their areas of expertise and interest. The information provided by registrants will be reviewed and selected individuals may be contacted to discuss their potential participation in the review. Any interested clinicians are encouraged to register for potential involvement in future opportunities, including initiatives through the Optimal Use and Therapeutic Review processes.

The following factors are considered when selecting clinical experts for participation in the review process:

- expertise regarding the diagnosis and management of the condition for which the drug is indicated
- conflict of interest declaration
- availability to commit to the review timelines
- regional representation (particularly for clinical panels).

7.4. Drug Program Engagement

7.4.1. Role of the Drug Programs

The drug programs provide input on each drug being reviewed through the reimbursement review processes by identifying issues that may impact their ability to implement a recommendation. This input increases the relevance of the recommendations and can potentially help avoid the need for an implementation advice panel or a request for advice later in the process by ensuring that potential implementation issues were considered during the review.

Examples of implementation considerations include, but are not limited to:

- variation in the reimbursement status and reimbursement conditions of comparator drugs across the drug programs
- potential for combination usage with other available therapies
- potential for adjusting the dosage over time
- potential issues with administration or distribution mechanisms (e.g., need for specialty clinics)
- challenges with diagnostic testing requirements.

7.4.2. Drug Program Input

7.4.2.1. Presubmission Phase

Representatives from the drug programs and pCPA may attend presubmission meetings.

Once advance notification for a pending application has been received, a lead jurisdiction is assigned using a rotational schedule of PAG members for oncology drugs and FWG members for non-oncology drugs. For drugs reviewed through the interim PPRP process, Canadian Blood Services will be the assigned as the lead jurisdiction.

The drug programs are notified regarding the pending application at the time advance notification has been received. The drug programs will be provided with the following information in the presubmission phase:

- the advance notification form
- the sponsor's completed proposed place in therapy template (for oncology drugs)
- an updated rotational schedule for lead jurisdictions.

7.4.2.2. Review Phase

The drug programs are provided with a copy of the documents filed by the sponsor. This will supplement the information provided in the presubmission phase, most notably with the submitted price, BIA, and implementation plan (in the case of a cell or gene therapy).

The lead jurisdiction will be tasked with preparing a draft summary of potential implementation considerations for discussion and finalization with other members of the advisory committees (i.e., PAG or FWG, as applicable). Input from the drug programs will be incorporated into the draft report for review and comment by the sponsor. Any comments related to the input from the drug programs will be made available to PAG or FWG for their consideration.

7.4.2.3. Recommendation Phase

The summary of implementation issues will be presented by the lead jurisdiction (or a designate) at the expert review committee. In the event the committee has questions regarding any potential implementation issues associated with a recommendation, the committee chair may ask the lead jurisdiction (or designate) to provide clarity for the committee. The drug programs are eligible to provide feedback and/or file a request for reconsideration of the draft recommendation. The draft recommendations will typically be discussed with PAG and FWG to collate and finalize their feedback.

Table 13: Key Milestones for Drug Program Engagement

Milestones	Description
Timing of drug program input	Drug programs will provide input early in the review phase (i.e., 10 to 15 business days after the file has been accepted for review)
Documents provided	Advance notification documentation followed by the complete application filed by the sponsor
Format for drug program input	A standardized template is provided for completion by the lead jurisdiction; the initial draft will be discussed and finalized at the next scheduled PAG or FWG meeting
Posting drug program input	Drug program input will be incorporated into the review report and posted publicly
Role at expert committee meeting	Lead jurisdiction would present a summary of the implementation issues identified by the drug programs and respond to inquiries from the committee members
Commentary on recommendations	Clinician groups will have 10 business days to review and comment on the draft recommendations during the feedback period; the drug programs are eligible to file a request for reconsideration
Implementation phase	Drug programs may request that an implementation advice panel be convened and participate in the process

FWG = Formulary Working Group; PAG = Provincial Advisory Group.

8. Application and Screening Procedure

By filing an application, the sponsor consents to be bound by the terms and conditions specified in the *Procedures for Reimbursement Reviews*, including the confidentiality guidelines and all provisions regarding withdrawal from the reimbursement review processes. Consent to the terms and conditions contained herein cannot be revoked by the sponsor at any time during or after the reimbursement review processes.

8.1. Application Filing

The application filed by the sponsor must adhere to the content, format, and organization stipulated in the current version of the *Procedures for Reimbursement Reviews* and any applicable *Pharmaceutical Reviews Updates*. All documents must be provided in English.

Sponsors must be registered with the Pharmaceutical Submissions SharePoint site before filing the required documents. For detailed information on how to register, please consult Pharmaceutical Submissions SharePoint Site – Setup Guide. Please ensure that both primary and secondary contacts, as well as any submitting consultants working on an application for a reimbursement review, are registered with the Pharmaceutical Submissions SharePoint site.

Requirements must be filed using the Pharmaceutical Submissions SharePoint site. The sponsor must upload 1 copy of all requirements to the corresponding review using the Pharmaceutical Submissions SharePoint site, per the file folder and file format specified in Appendix 6. Requirements must be filed using the Pharmaceutical Submissions SharePoint site during business hours (between 8:00 a.m. and 4:00 p.m. Eastern time). If filed outside of business hours, the next business day will be considered the date of transmittal.

An acknowledgement of receipt is sent to the sponsor to confirm that the requirements have been received. Sponsors that experience difficulties filing documents with the Pharmaceutical Submissions SharePoint site should contact CDA-AMC for support or to arrange an alternate delivery method (e.g., by email or mailing a USB flash drive).

Copies of the requirements will be provided to the drug programs to ensure that they have this information prior to the targeted expert committee meetings. Sponsors are still required to provide copies of their application — including all drug program–specific requirements — to the individual drug programs (i.e., requirements are not provided on behalf of the sponsor).

8.2. Application Screening

The following provisions apply to all applications filed by sponsors or drug programs.

- The Pharmaceutical Submissions SharePoint site logs the date and time that the requirements are received.

- Applications are accepted on an ongoing basis and are screened in the order they are received.
- The date of receipt is considered day zero for the purpose of calculating the 10–business day targeted time frame for initial screening of requirements.
- If the filed requirements are deficient or require revision, a notice is sent to the sponsor advising what information needs to be included or revised to be accepted for review. Rescreening of the requirements is completed as soon as possible after receiving them but may take up to 5 business days.
- On day 10 of the screening period, a letter is sent to the sponsor advising whether the requirements have been accepted for review.
- Following an acceptance for review, the sponsor must also provide the requirements to all of the drug programs that require copies (refer to Contact Information and Requirements for Drug programs for details).

8.3. Review Initiation

8.3.1. Application Fees

All applications filed by manufacturers are subject to an application fee. For details, please consult the *Fee Schedule for Pharmaceutical Reviews*.

As stated in the *Fee Schedule for Pharmaceutical Reviews*, a case-by-case assessment is made regarding the application fee when there are multiple indications included in one application. Multiple fees are assessed to ensure that the application fee accurately reflects the level of effort and resources required to review the application. This decision is based on the following 4 factors:

- The indications are sufficiently different to require consultation with different clinical specialists.
- The indications are best addressed through separate review reports and/or expert committee recommendations.
- The indications have been studied in separate clinical development programs (e.g., separate clinical trials for each population).
- The sponsor has filed different economic analyses and budget impact analyses for each of the indications.

The final decision is made based on the considerations noted above. It is important to note that not all the factors need to be met for an application to warrant multiple application fees.

Any sponsors that are uncertain about the application fees are encouraged to contact CDA-AMC early in the presubmission phase to seek guidance.

8.3.2. Ordering of Applications

All applications will be assigned to the work schedule on a first-come, first-served basis, as determined by the date of acceptance for review, except for requests for advice. Reviews are typically initiated within 10 business days of acceptance for review. Key dates (including initiation and the targeted expert committee meeting) are provided to the sponsor only once the requirements have been accepted for review. CDA-AMC posts the targeted meeting dates on which applications may be considered if their reviews are initiated by a given date.

8.3.3. Review Team

The unique composition of each review team is established based on the nature of the review and in consideration of the proposed team members' qualifications, expertise, and compliance with the CDA-AMC Conflict of Interest Policy. Except for the review manager(s), the names of the review team members, including members of clinical expert panels (if applicable), will not be disclosed to the sponsor.

8.4. New Information Filed in the Review Phase

8.4.1. Finalized Information for Submissions Filed on a Pre-NOC Basis

For submissions filed on a pre-NOC basis, some requirements will be outstanding or not finalized at the time that the submission is filed (e.g., product monograph). The sponsor must provide all outstanding and/or finalized requirements as soon as they are available.

The finalized information is assessed upon receipt. Depending on the nature and extent of changes to the information compared with what was originally filed, the timelines required to review it and incorporate it into the review report will be determined. This could result in the submission being considered at a later expert committee meeting. In the event the finalized information is received after the drug has been discussed by the expert committee, the information will be reviewed, and it will be determined if the draft recommendation will be issued or if the drug should be placed on the agenda for a subsequent meeting of the expert committee. The sponsor will be notified of any revisions to the anticipated timelines. If additional supporting documentation is required, the sponsor will be notified of the requirements.

Once the sponsor has been notified that the finalized requirements have been accepted, the sponsor must ensure that the drug programs are provided with a copy of the finalized requirements.

8.4.2. New Information Filed Before Draft Report Sent to Sponsor

During all reviews, CDA-AMC will determine whether additional information from the sponsor is needed to complete the review. If so, the sponsor will be contacted. Delays in providing the requested information may result in a temporary suspension of the review due to incomplete information to conduct

a thorough review (refer to section 12). If a sponsor submits updated information for inclusion in an ongoing review (i.e., after the requirements have been accepted and the review has been initiated), the timeline required to review the new information and incorporate it into the review report will be determined. This could result in the application being considered at a later meeting of the expert committee. The sponsor would be apprised of any revisions to the anticipated timelines for the review.

No new clinical studies may be submitted after the application has been accepted for review by CDA-AMC (unless the application is being reviewed through the rolling submission pilot and the content and timelines have been discussed and approved by CDA-AMC prior to filing the submission).

Sponsors are strongly discouraged from filing revised economic models after an application has been accepted for review. The only exceptions are situations where CDA-AMC has identified important limitations that prevent a robust appraisal of the sponsor's economic evaluation (i.e., in accordance with the process outlined in section 6.12.1).

If a sponsor identifies an issue in an economic model or budget impact model that has already been accepted, the sponsor must promptly notify CDA-AMC of the issue. The sponsor is required to submit a detailed summary of the changes required to address the error (e.g., Log of Model Changes) in addition to a corrected model. CDA-AMC discourages drug sponsors from submitting new model files without notifying CDA-AMC in advance.

8.4.3. New Information Filed After Draft Report Sent to Sponsor

No new information can be filed after the draft review report has been sent for sponsor review and comment. This includes, but is not limited to:

- new economic models
- new economic evaluations
- new submitted price
- new clinical studies (i.e., those not included in the initial application package)
- new data cut-offs or other analyses for studies included in the review report
- new indirect treatment comparisons.

Any sponsors who wish to file new information after receiving the draft review report will be required to formally withdraw and refile their application with section 12.

8.5. Rolling Submission Pilot

In a rolling review submission, a review is initiated earlier, and evidence is submitted as it becomes available rather than waiting for all the required documentation to be assembled into a single application package. CDA-AMC announced an expanded rolling review process pilot that may include any drug application that is filed before Health Canada's regulatory decision (if the sponsor consents to

information-sharing between CDA-AMC and Health Canada). The overall objective of the rolling submission pilot process is to facilitate a reimbursement recommendation earlier than would be possible if the sponsor waited until all documentation was ready to initiate the review process.

8.5.1. Eligibility Criteria for Rolling Submissions

The criteria described in Table 14 are used to determine eligibility for the rolling submission pilot. The rolling submission pilot will only be an option for standard and complex reviews (tailored reviews will not be eligible for the pilot process).

Table 14: Eligibility Criteria for Rolling Submissions

Criteria for acceptance	Rationale for criterion
Regulatory approval status	
Applications must be filed before Health Canada's regulatory decision.	The pilot is focused on encouraging uptake of the pre-NOC submission process and will not be offered for submissions filed on post-NOC submissions.
Regulatory status	
The anticipated Health Canada date of decision must be known by the applicant (e.g., files undergoing consideration or reconsideration for priority review will not be approved for a rolling submission).	During this initial expansion of the rolling submission process, CDA-AMC must craft customized project schedules, and we will require a clear date for the Health Canada decision. In addition, to evaluate if the proposed rolling submission will achieve the goals of the Target Zero initiative, the regulatory decision date must be known from the outset of the project.
Regulatory review pathway	
Files undergoing review through an accelerated pathway will be prioritized for the initial expansion of the rolling submission process.	Acceptance through an accelerated regulatory review pathway reflects Health Canada's perspective that the drug may offer added clinical benefit in an area where there is unmet clinical need in Canada. We have heard from industry representatives that these applications can be the most challenging to file in accordance with the timelines needed to achieve Target Zero and that rolling submissions could help facilitate the parallel regulatory and CDA-AMC review.
Consent to information-sharing	
The sponsor must consent to information-sharing between Health Canada and CDA-AMC.	Consenting to information-sharing offers important efficiencies for CDA-AMC and is required to ensure that CDA-AMC can build upon the regulatory review for these applications.

Criteria for acceptance	Rationale for criterion
Alignment with objective of Target Zero	
Based on the anticipated Health Canada date of decision, the interval between Health Canada approval and the draft CDA-AMC recommendation would be shorter under the rolling submission process than under the standard process.	The primary objective of the rolling submission process is to reduce the interval between Health Canada approval and the draft CDA-AMC recommendation.
Rationale for the delayed application filing	
The sponsor must provide an acceptable rationale for why the application materials cannot be submitted in a single package and justify the length of time required to provide the information (e.g., the sponsor provides the target date that additional clinical information will be available to complete their economic application materials).	We will not accept a scenario in which a sponsor seeks additional time to complete an application or has encountered challenges with a vendor, at the expense of the time CDA-AMC would have to review the application.
Reduced timelines for sponsor review of draft report	
The sponsor must consent to a reduction in their timelines for review of the draft report (from 7 business days to 4 business days).	To implement a rolling submission, CDA-AMC will likely have to condense review timelines for selected portions of the review.
Performance metric	
The sponsor must agree to waive the 180–calendar day performance metric.	CDA-AMC will strive to deliver the draft recommendation as soon as possible, but we cannot guarantee that the performance metric can be achieved with a rolling submission. This may change in the future as we gain additional experience with these files.
Pharmacoeconomic model	
A pharmacoeconomic decision model (electronic file) should be filed with the initial application package. In cases where model parameter estimates (e.g., relative clinical efficacy, costs, utility estimates) are not complete, these parameters can be assigned placeholder values. The model must meet all screening requirements. As with standard submissions, a Pharmacoeconomic Technical Report should be filed, with placeholder values clearly identified (e.g., highlighted).	Filing beyond the 20–business day window could create challenges in the project schedule with respect to alignment of reviewing clinical and economic evidence and engagement with clinical specialists and will likely have consequences for the ability of CDA-AMC to complete our review within the anticipated timeline. In general, filing application materials closer to the 20–business day window will increase the likelihood that the submission will be placed on the agenda for the target expert committee meeting.

Criteria for acceptance	Rationale for criterion
An updated pharmacoeconomic model and report should be filed within approximately 20 business days after the file has been submitted to CDA-AMC. A log of changes made to the original file should also be filed. Failure to submit a completed model by the agreed-upon deadline may necessitate moving to a later expert committee meeting.	
Budget impact model and reports	
Sponsors will strongly be encouraged to file the budget impact model and reports as part of the initial application package. Sequential filing of this information will only be permitted if the sponsor provides clear rationale (e.g., data to inform treatment duration is pending from a clinical study).	Filing beyond the 20–business day window could create challenges in the project schedule with respect to alignment of reviewing clinical and economic evidence and engagement with clinical specialists and will likely have consequences for the ability of CDA-AMC to complete our review within the anticipated timeline. In general, filing application materials closer to the 20–business day window will increase the likelihood that the submission will be placed on the agenda for the target expert committee meeting.
Clinical information	
In general, all clinical and administrative requirements should be filed with the initial application package. This includes, but is not limited to: • pivotal clinical data • comparative evidence (direct or indirect comparison[s]) • studies addressing gaps in the clinical evidence.	Filing beyond the 20–business day window could create challenges in the project schedule with respect to alignment of reviewing clinical and economic evidence and engagement with clinical specialists and will likely have consequences for the ability of CDA-AMC to complete our review within the anticipated timeline. In general, filing application materials closer to the 20–business day window will increase the likelihood that the submission will be placed on the agenda for the target expert committee meeting.

CDA-AMC = Canada's Drug Agency; NOC = Notice of Compliance.

8.5.2. Presubmission Phase

Sponsors may request a presubmission meeting to discuss eligibility for the rolling submission pilot. Advance notification must be provided in accordance with the requirements outlined in section 4.2.

8.5.3. Application Phase

Sponsors who are interested in participating in the rolling submission pilot must proactively notify CDA-AMC and receive confirmation of eligibility before submitting their advance notification for the pending

application. Those interested in the rolling submission pilot must complete the application form and submit it to CDA-AMC using the Pharmaceutical Submissions SharePoint site. Before issuing a decision regarding eligibility, we may require that the sponsor participate in a presubmission meeting to allow for more in-depth discussion on the application.

8.5.4. Screening Phase

CDA-AMC will examine the sponsor's application and confirm whether the drug under review meets the eligibility criteria for the rolling submission process. CDA-AMC will notify sponsors within 10 business days of filing the rolling submission application form. The sponsor will be informed if additional time is required to screen the rolling submission application.

Drugs that are not eligible to be considered through the rolling submission process would be screened and accepted according to the existing reimbursement review procedures. Any sponsors who disagree with the eligibility decision should contact CDA-AMC with complete details regarding why the sponsor believes the incorrect decision was made. CDA-AMC will work with these sponsors on a case-by-case basis to clarify or revise the eligible decision as required.

8.5.5. Target Time Frames

As with all Reimbursement Reviews, the key targeted time frames and the status for rolling submissions will be posted on the project webpage. The review timelines will be determined on a case-by-case basis and will depend on the complexity of the economic submission and the timeline for filing the information. Depending on the volume or complexity of the material filed by the sponsor after acceptance for review (i.e., the updated or finalized information submitted as part of the rolling submission process), an extension of the review time frame may be required. The sponsor will be notified of any extensions, as well as the reasons for the extensions. To minimize the risk of extending the review timelines, it is important that the sponsor clearly communicate their plan to file additional information during the review and avoid substantial revisions to the economic model.

CDA-AMC will strive to deliver the draft recommendation in accordance with the performance metrics outlined in the Fee Schedule for Pharmaceutical Reviews (i.e., ≤ 180 calendar days from the date the file is accepted for review to the date the draft recommendation is issued to the sponsor and drug programs). However, as the application materials will be filed sequentially for a rolling submission, the sponsor will be required to waive the performance metric for any application filed through the rolling submission process. This is required because extensions to the review timelines may be necessary for reasons that are outside the control of CDA-AMC. The procedures for temporary suspension and withdrawal outlined in section 12 will also apply for rolling submissions.

8.5.6. Call for Patient and Clinician Group Input

The timelines for the call for patient and clinician group input will be the same as all other applications (i.e., a 35-business day call for input that will begin 29 business days before the target date for the application to be filed with CDA-AMC).

8.5.7. Review Phase

The review of applications filed through the rolling submission process will be conducted in the same manner as other applications but using a customized project schedule to reflect the sequential filing and review of application materials. The draft review report will not be sent to the sponsor until all outstanding application materials have been filed and reviewed by the sponsor (except for documentation that is awaiting finalization through the regulatory review process [e.g., final product monograph]).

8.5.8. Recommendation Phase

Applications that are accepted for review through the rolling submission pilot will only be placed on the agenda when the sponsor has filed all outstanding application requirements (except for documentation that is awaiting finalization through the regulatory review process). The recommendation will be issued by the existing drug expert committees (i.e., CDEC or pERC, as applicable). Draft recommendations will be posted for feedback in accordance with the existing Reimbursement Review procedures.

8.5.9. Evaluation of the Pilot

We will evaluate the rolling submission pilot after 1 to 2 years to ensure it is having the intended impact. We will continue to engage with industry members throughout the pilot to seek opportunities for greater clarity and identify additional opportunities where the process can further the objectives of the Target Zero initiative.

9. Evidence Review Procedures

9.1. Standard Review

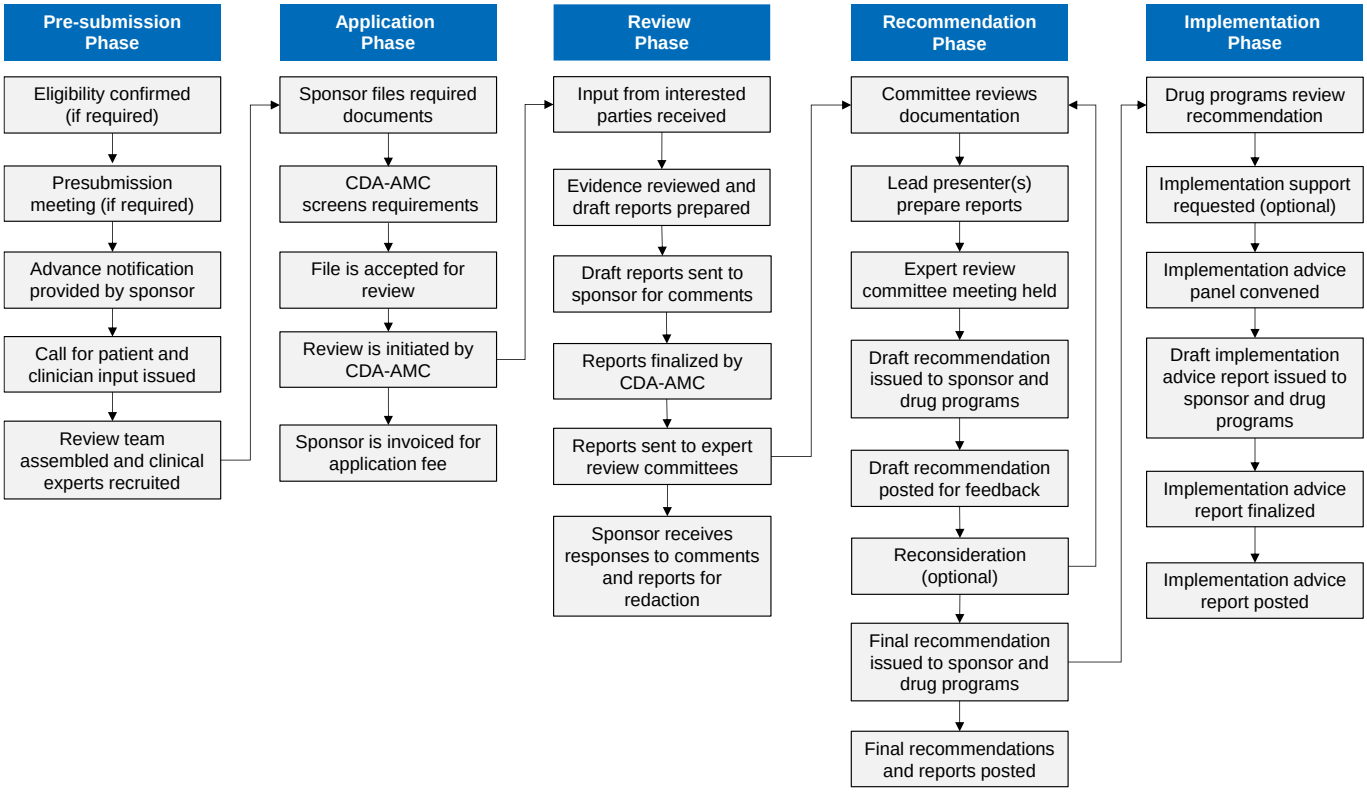
This section describes the reimbursement review procedures for standard reviews (summarized in Figure 3). CDA-AMC prepares a main review report summarizing the following key information:

- background on the disease condition and the drug under review
- input from patient groups, clinician groups, and clinical experts consulted by CDA-AMC
- input from public drug programs regarding implementation considerations for the drug under review
- appraisal and interpretation of the comparative clinical effectiveness of the drug under review
- appraisal and re-analyses of the pharmacoeconomic evaluation and budget impact analysis

- ethics and equity considerations relevant to the disease condition and drug under review.

In addition to the review report, CDA-AMC will prepare a supplemental material document with appendices and supporting information referred to in the main review report. The report is prepared in accordance with a template (main report template and supplemental material template) and is finalized in accordance with section 10.

Figure 3: Overview of Procedure for Standard and Complex Review



9.1.1. Target Time Frames

The key targeted time frames and the status of all reviews are posted on the CDA-AMC website. Table 15 indicates the targeted time frames for key tasks within the reimbursement review process for standard and complex reviews. Depending on the volume or complexity of the material to be reviewed, an extension of the review time frame deadlines may be required. The sponsor will be notified of any extensions, as well as the reasons for the extensions. Target timelines for all reviews, including those eligible for a time-limited reimbursement recommendation, reflect the performance metrics outlined in the Fee Schedule for Pharmaceutical Reviews (i.e., ≤180 calendar days from the date the file is accepted for review by CDA-AMC to the date the draft recommendation is issued to the sponsor and drug programs).

Table 15: Targeted Timelines for the Standard and Complex Reviews

Key milestone	Business days
Application and Screening Phase	
Application received	0
Requirements screened for acceptance	10
Review initiated	1 to 10
Evidence Review Phase	
Draft report and supplemental material are prepared and sent to sponsor for comments	53[a]
Sponsor reviews draft report and supplemental material and provides comments	7
Responses to comments[b] and revised report prepared (as required)	8
Draft Recommendation Phase	
Committee reviews materials and prepares presenter reports	10
Expert committee meeting	1 to 2
Draft recommendation issued to drug programs and sponsor	8 to 10
Sponsor identifies confidential information	2
Redaction of confidential information	1
Validation of redactions by the sponsor	1
Draft recommendation posted for feedback	2
Feedback period	10
Request for reconsideration	Variable[c]
Final Recommendation Phase	
Final recommendation issued to drug programs and sponsor (no reconsideration) Final recommendation issued to drug programs and sponsor (after reconsideration)	8 to 10 8 to 10
Sponsor requests redaction of confidential information in recommendation	2
Redaction of confidential information in recommendation	1
Validation of redactions by the sponsor	1[d]
Final recommendation copy-edited and formatted for posting	7
Final recommendation posted on website	1

[a] In the case of a disagreement expressed by the sponsor regarding redactions made in the review report, additional time may be required to resolve the disagreement in consultation with the sponsor. This additional time could delay publication of the review report and/or recommendation.

[b] Sponsors will be sent responses and the revised reports 8 business days prior to the expert committee meeting.

[c] The time frame required to address the request for reconsideration depends on the amount of work needed to address the request, as well as the available dates for expert committee meetings.

[d] In the case of a disagreement expressed by the sponsor regarding redactions made in the review report, additional time may be required to resolve the disagreement in consultation with the sponsor. This additional time could delay publication of the review report and/or recommendation.

9.1.2. Clinical Review

9.1.2.1. Information Considered

The clinical section of the report is based on the sponsor summary of clinical evidence template, source documentation provided by the sponsor, and input from interested parties. Strengths and limitations with respect to both internal validity (i.e., how well the study was designed, conducted, and reported) and external validity (i.e., how well the results of the study could be applied to the target population in Canada) are documented.

9.1.2.2. List of Studies and Efficacy Outcomes

A list of the studies and a list of the efficacy outcomes that will be included in the clinical review are sent to the sponsor for information purposes and to assist the sponsor in preparing to review and provide comments on the draft report. CDA-AMC summarizes and critically appraises the relevant evidence.

9.1.2.3. Input From Patients and Clinicians

Commentary in the clinical report regarding the potential place in therapy of the drug under review is provided by 1 or more clinical specialists with expertise in the diagnosis and management of the condition for which the drug is indicated.

Patient and clinician group input are summarized in the report. When discussing the available evidence, CDA-AMC reflects on the input from patient and clinician groups, particularly any areas where there is an unmet therapeutic need for those living with the condition; known advantages and disadvantages of the treatments that are currently available; and any expectations regarding new therapies (including the drug under review). Refer to sections 7.2 and 7.3 for additional details on patient group and clinician involvement, respectively.

9.1.2.4. Ethics and Equity Considerations

The report will raise ethics and equity considerations that are relevant to the indication and drug under review. These may include but are not limited to: disproportionate disease burden on equity-deserving groups, adequate representation of diverse groups in available evidence, equity of access to current or existing treatments, ability of patients to equitably access the drug under review, nonclinical treatment burdens for patients or caregivers, and considerations related to privacy, confidentiality, and patient autonomy or dignity.

9.1.2.5. Considerations for a Time-Limited Recommendation

Applications that are eligible for consideration through the time-limited reimbursement recommendation will include the additional considerations noted below will be incorporated into the review process and applicable CDA-AMC reports.

Consideration of Evidence Gaps

The CDA-AMC report will note the gaps in the evidence as identified by the sponsor within the evidence-generation plans (and confirmed within the Qualifying Notice, once available), in addition to other gaps that may be identified during the review and recommendation phases. As part of the appraisal and interpretation of the evidentiary package filed by the sponsor, the potential importance of the gaps in the evidence will be discussed with clinical specialists who have experience treating and managing the condition in Canada. The sponsor will have the opportunity to review and comment on the draft report, including commentary related to evidence gaps, before the expert committee meeting.

Qualifying Notice

In the case of an aligned review with Health Canada, both the sponsor and Health Canada may upload the draft Qualifying Notice to CDA-AMC. To avoid any potential delays, the onus will always be on the sponsor to provide CDA-AMC with the draft and final Qualifying Notice once available (i.e., Health Canada may provide this information to help accelerate the review, but they are not responsible for ensuring that CDA-AMC receives the information).

For applications filed on a pre-NOC) basis, the review report will not be completed until the details of the qualifying notice for the NOC/c have been provided to CDA-AMC, as described in Table 16. This is required to ensure that all relevant information is available at the time of the committee's deliberations. If there is any uncertainty regarding the evidence generation plans, the sponsor will be contacted by CDA-AMC and requested to provide additional details.

As with all finalized information for an application filed on a pre-NOC basis, CDA-AMC will assess the Qualifying Notice upon receipt. Depending on the nature and extent of changes to the information compared with what was originally filed and communicated to CDA-AMC regarding the evidence

generation plans, CDA-AMC will determine the timelines required to review it and incorporate it into the review report. This could result in the submission being considered at a later expert committee meeting.

Table 16: Requirements for Qualifying Notice

Aligned review participation[a]	Documentation required by CDA-AMC
Application filed on a post-NOC/c basis	
Not applicable	The final qualifying notice issued by Health Canada must be included in the application package.
Application filed on a pre-NOC basis	
Sponsors who opt into the information-sharing process between CDA-AMC and Health Canada	CDA-AMC receives confirmation from Health Canada and the sponsor that the content of the qualifying notice has been determined. A draft of the qualifying notice is provided to CDA-AMC as soon as content has been determined.
Sponsors who do not opt into the information-sharing process between CDA-AMC and Health Canada	The final qualifying notice issued by Health Canada must be submitted to CDA-AMC by the sponsor.

NOC = Notice of Compliance; NOC/c = Notice of Compliance with Conditions.

[a] An optional information-sharing process for submissions filed on a pre-NOC basis has been established to permit Health Canada and CDA-AMC to exchange information related to the drug under review.

9.1.3. Economic Review

At the initiation of the process, the economic reviewers work with the clinical reviewers to ensure that clinical information pertinent to the economic review is considered within the clinical review. The economic review is conducted in line with the Guidelines for the Economic Evaluation of Health Technologies: Canada. CDA-AMC reviews the sponsor's pharmacoeconomic report and economic model, and critically appraises the sponsor's methods, inputs, and assumptions. As part of this appraisal, this entails:

- The model structure, assumptions, and inputs are validated through consultation with the clinical reviewers and clinical expert(s) involved in the review to ensure the information in the economic model aligns with existing Canadian practice and the findings of the clinical review.
- The patient input that was received is considered, including whether or how the information identified has been incorporated in the economic submission.
- The sponsor's submitted economic model is tested to confirm the reproducibility of the probabilistic results and to identify any key drivers of the model results.
- Reanalyses are conducted to address the limitations noted with the sponsor's model to provide revised results (i.e., CDA-AMC base-case reanalysis). If reanalyses are not possible, CDA-AMC will comment on the potential impact of such limitations to the economic findings.

The report will include a cost comparison table of the treatments indicated and/or used for the condition in the Canadian setting.

A model change log will be shared with relevant partners as a separate document that details specific changes made to sponsors' models, aligned with the steps described in the CDA-AMC pharmacoeconomic report, to derive the CDA-AMC base case.

9.1.4. Companion Diagnostic Review

For submissions that include companion diagnostics, the reimbursement review process will include the following additional considerations.

9.1.4.1. Testing Procedure Assessment

Through the Eligibility Application for a Testing Procedure Assessment section of the consolidated eligibility form, CDA-AMC will collect from the sponsor information about the companion diagnostic(s) or other testing associated with the drug. Based on that and any other information identified by the review team, CDA-AMC will determine if the testing procedure is anticipated to raise implementation considerations and have new impacts on health systems (e.g., new biomarker or first application of an existing testing procedure to the disease or condition). If so, CDA-AMC will conduct a full testing procedure assessment and provide it as a separate section of the main report. Otherwise, CDA-AMC will produce a brief summary of the testing procedure considerations and include it in the introduction of the main report.

CDA-AMC will assess the following for each relevant testing procedure:

- Health system-related considerations (e.g., number of individuals in Canada expected to require the testing procedure, availability and reimbursement status of the testing procedure in jurisdictions across Canada, whether the testing procedure is currently part of routine care, repeat testing requirements, impacts on human and other health care resources by provision of the testing procedure)
- Patient-related considerations (e.g., accessibility of the testing procedure in jurisdictions across Canada, expected turnaround times for the testing procedure, burden associated with the testing procedure for patients, families, and/or caregivers)
- Clinical considerations (e.g., clinical utility and validity of the testing procedure, risks of harm associated with the testing procedure)
- Cost considerations (e.g., projected cost of the testing procedure)

CDA-AMC will evaluate the sponsor-provided reference list and copies of articles that highlight the clinical validity and utility of the companion diagnostic(s) under review and may conduct a separate search of the clinical validity and utility of the companion diagnostic(s).

9.1.4.2. Economic Evidence

As part of the appraisal of the sponsor-provided pharmacoeconomic evaluation, CDA-AMC will consider the costs and consequences of any required biomarker testing that sponsors incorporate into the submitted analyses.

9.1.4.3. Patient Input

The patient input template asks patient groups to comment on their expectations and/or experiences with any required biomarker testing for the drug under review. Patient groups are asked to consider answering this question for eligible drugs that have companion diagnostics.

9.1.4.4. Clinician Input

As part of engaging expert clinicians throughout the review process, CDA-AMC may reach out to additional experts in pathology and/or laboratory testing who would be able to comment on front-line clinical aspects of the companion diagnostic(s) (e.g., the timing of biomarker testing in the clinical care pathway, the consistency of the testing protocol with current practice, and the availability of the testing).

9.1.4.5. Jurisdictional Input

As part of soliciting implementation considerations from its participating jurisdictions, CDA-AMC will also seek insights into the enablers and barriers related to any required biomarker testing.

9.2. Complex Review

9.2.1. Target Time Frames

The key targeted time frames and the status of all reviews are posted on the CDA-AMC website.

Table 15 indicates the targeted time frames for key tasks within the reimbursement review process for a complex review. Depending on the volume or complexity of the material to be reviewed, an extension of the review time frame deadlines may be required. The sponsor will be notified of any extensions, as well as the reasons for the extensions. Target timelines for all reviews, including those eligible for a time-limited reimbursement recommendation, reflect the performance metrics outlined in the Fee Schedule for Pharmaceutical Reviews (i.e., ≤ 180 calendar days from the date the file is accepted for review by CDA-AMC to the date the draft recommendation is issued to the sponsor and drug programs).

9.2.2. Process Enhancements for Complex Reviews

Table 17 summarizes how process enhancements are applied in the complex review process to address specific challenges that may be posed by the drug under review.

Table 17: Process Enhancements for Complex Drug Reviews

Process enhancements[a]	Scenario 1: First drug indicated in therapeutic area	Scenario 2: Priority review drugs that are not the first approved in the therapeutic area[b]	Scenario 3: Primary end point is a novel surrogate outcome	Scenario 4: Tumour-agnostic therapies	Scenario 5: Additional studies only[c]
Enhanced clinician engagement	Included	Included	Included	Included	Additional studies may be included in an application that does meet the criteria outlined in scenarios 1 to 4 provided the studies address important gaps in the submission.
Person with lived experience	Included	Included	Only if criteria for scenarios 1 or 2 are also met		
Separate ethics review[d]	May be included	Not included			
Additional consultation with methodologists	May be included	May be included	Included	Included	
Consideration of additional studies that address gaps[c,e]	May be included	May be included	May be included	May be included	Included

[a] Canada's Drug Agency is conducting an ongoing pilot on the use of societal perspective in economic evaluations. The eligibility criteria for the inclusion of a societal perspective in complex drug reviews may change as a result of this pilot, which is expected to conclude in July 2025. Please refer to section 9.2.2.4 for further details regarding the current eligibility criteria.

[b] These are intended to include drugs with the potential to alter the treatment paradigm based on superior efficacy and/or safety. These must be accepted by Health Canada for review through its priority review pathway.

[c] Scenario 5: As noted in the consultation document, additional studies may be included in an application that does meet the criteria outlined in scenarios 1 to 4 provided the studies address important gaps in the submission. These applications will be subject to a Schedule E application fee and will not have the additional process enhancements outlined in this table, except for the review and recommendation phases including consideration of the additional evidence.

[d] Some drugs that meet the criteria for a complex review based on the patient population (as previously outlined) may pose ethical challenges for the expert committee and/or decision-makers and warrant a dedicated and more in-depth review of ethical considerations. This may include novel drugs from the following classes: cell therapies, gene therapies, radiopharmaceuticals, prenatal interventions, public health or preventive interventions, interventions limited by health system capacity, or other therapies that are ethically complex across multiple dimensions (e.g., raising notable risks of serious adverse events and uncertain benefit, therapies primarily impacting structurally marginalized populations).

[e] Any application that meets the criteria outlined in scenarios 1 to 4 may include additional studies that address important gaps in the clinical trial or comparative evidence (direct or indirect) submitted by the sponsor.

9.2.2.1. Enhanced Clinician Engagement

For complex reviews meeting the criteria for scenarios 1, 2, 3, and 4, CDA-AMC will typically include 2 to 3 clinical specialists as part of the review team and a panel with additional clinical specialists may be convened (as described in section 7.3.2).

9.2.2.2. Person With Lived Experience

For complex reviews meeting the criteria for scenarios 1 and 2, CDA-AMC will seek to engage a person with experience with the condition for which the drug under review is indicated (i.e., a patient, caregiver, or family member) to participate in the expert committee meeting by delivering a brief presentation and answering questions from the committee members. This process is described in detail in section 7.2.3.

9.2.2.3. Ethics Review

Some drugs that meet the criteria for a complex review based on the patient population (as previously outlined) may pose ethical challenges for the expert committee and/or decision-makers and warrant a dedicated and more in-depth review of ethical considerations. This may include novel drugs from the following classes: cell therapies, gene therapies, radiopharmaceuticals, prenatal interventions, public health or preventive interventions, interventions limited by health system capacity, or other therapies that are ethically complex across multiple dimensions (e.g., raising notable risks of serious adverse events and uncertain benefit, therapies primarily impacting structurally marginalized populations).

For the drug under review, CDA-AMC will identify and describe relevant ethical considerations across 4 domains:

- indicated population(s)
- evidentiary basis
- use and implementation
- health systems considerations.

CDA-AMC determines the scope, content, and format of the ethics component for complex reviews based on the complexity and breadth of ethical considerations present.

9.2.2.4. Societal Perspective

CDA-AMC is evaluating the use of the societal perspective in economic evaluations through an ongoing pilot that is expected to conclude in July 2025. During this pilot period, economic evaluations that include the societal perspective as a second base case will continue to be accepted for applications that meet the criteria initially specified in the pilot announcement:

- cell and gene therapies
- drugs that are first-in-class

- drugs reviewed through Health Canada's expedited pathways
- drugs that have an undefined place in therapy.

Eligibility and procedures for submitting evaluations using a societal perspective will be further refined following the pilot, based on lessons learned.

9.2.3. Clinical Review

The review of clinical evidence will occur in the same manner as described for the standard review process in section 9.1.2.

9.2.4. Economic Review

The review of economic evidence will occur in the same manner as described for the standard review process in section 9.1.3.

9.2.5. Companion Diagnostic Review

For submissions that include companion diagnostics, the reimbursement review process will include the process described in section 9.1.4.

9.3. Tailored Review

9.3.1. Target Timeframes

The key targeted time frames and the status of all reviews are posted on the CDA-AMC website. Table 18 indicates the targeted time frames for key tasks within the reimbursement review process for tailored reviews. Depending on the volume or complexity of the material to be reviewed, an extension of the review time frame deadlines may be required. The sponsor will be notified of any extensions, as well as the reasons for the extensions. The timelines listed in Table 18 are the target for CDA-AMC. The performance metrics outlined in the *Fee Schedule for Pharmaceutical Reviews* apply to tailored reviews (i.e., ≤ 180 calendar days from the date the file is accepted for review by CDA-AMC to the date the draft recommendation is issued to the sponsor and drug programs).

Table 18: Targeted Timelines for Tailored Reviews

Key milestone	Business days
Application and screening phase	
Application received	0
Requirements screened for acceptance	10
Review initiated	1
Evidence review phase	
Draft report prepared and sent to sponsor for comments	35 to 38

Key milestone	Business days
Sponsor reviews draft report and provides comments	5
Responses to comments[a] and revises report (as required)	6 to 11
Draft recommendation phase	
Distribution of briefing materials and review by subcommittee members	10
Expert committee or subcommittee meeting	1 to 5
Draft recommendation issued to drug programs and sponsor	8 to 10
Sponsor identifies confidential information	2
Redaction of confidential information	1
Validation of redactions by the sponsor[b]	1
Draft recommendation posted for feedback	2
Feedback period	10
Request for reconsideration	Variable[c]
Final recommendation phase	
Final recommendation issued to drug programs and sponsor (no reconsideration) Final recommendation issued to drug programs and sponsor (after reconsideration)	8 to 10 8 to 10
Sponsor requests redaction of confidential information in recommendation	2
Redaction of confidential information in recommendation	1
Validation of redactions by the sponsor[b]	1[d]
Final recommendation copy-edited and formatted for posting	7
Final recommendation posted on website	1

[a] Sponsors will be sent responses and the revised reports 8 business days before the expert committee meeting.

[b] In the case of a disagreement expressed by the sponsor regarding redactions made in the review report, additional time may be required to resolve the disagreement in consultation with the sponsor. This additional time could delay publication of the review report and/or recommendation.

[c] The time frame required to address the request for reconsideration depends on the amount of work needed to address the request, as well as the available dates for expert committee meetings.

9.3.2. Clinical Review

9.3.2.1. Information Considered

CDA-AMC validates and critically appraises the information provided by the sponsor within the submission template. Strengths and limitations with respect to both internal validity (i.e., how well the study was designed, conducted, and reported) and external validity (i.e., how well the results of the study could be applied to the target population in Canada) are documented. CDA-AMC includes its assessment of the submitted information and comments directly in the appropriate sections of the tailored review template. The review report for a tailored review is finalized in accordance with section 10.

9.3.2.2. Input From Patients and Clinicians

The patient group input is summarized in the report. When discussing the available evidence, CDA-AMC reflects on the input from patient groups, particularly any areas in which there is an unmet therapeutic need for those living with the condition, known advantages and disadvantages of the treatments that are currently available, and any expectations expressed by patients regarding new therapies (including the drug under review). Refer to section 7.2 for additional details on patient engagement in the reimbursement review process.

All review teams typically include at least 1 clinical expert who provides guidance and interpretation throughout the review. Commentary in the clinical report regarding the potential place in therapy of the drug under review is provided by 1 or more clinical specialists with expertise in the diagnosis and management of the condition for which the drug is indicated. Refer to section 7.3 for additional details on clinical expert involvement in the reimbursement review process.

9.3.3. Economic Review

9.3.3.1. PACES Tailored Review

At the initiation of the process, the economic reviewers work with the clinical reviewers to ensure that clinical information pertinent to the economic review is considered within the clinical review. The economic review is conducted in line with the *Guidelines for the Economic Evaluation of Health Technologies: Canada*. CDA-AMC reviews the sponsor's pharmacoeconomic report and cost calculations Excel workbook, and critically appraises the sponsor's methods, inputs, and assumptions. This appraisal entails:

- The assumptions and inputs are validated through consultation with the clinical reviewers and clinical expert(s) involved in the review to ensure they align with existing practice in Canada and the findings of the clinical review.
- The patient input that was received is considered, including whether or how the information identified has been incorporated in the economic submission.
- The sponsor's submitted Excel workbook is tested to confirm the reproducibility of the results and to identify any key drivers of the model results.
- Reanalyses are conducted to address the limitations noted with the sponsor's model to provide revised results (i.e., CDA-AMC base-case reanalysis). If reanalyses are not possible, CDA-AMC will comment on the potential impact of such limitations on the economic findings.

The report will include a cost comparison table of the treatments indicated and/or used for the condition in Canada.

A model change log will be shared with relevant partners as a separate document that details specific changes made to the sponsor's models, aligned with the steps described in the CDA-AMC pharmacoeconomic report, to derive the CDA-AMC base case.

9.3.3.2. Product Variation Tailored Review

At the initiation of the process, the economic reviewers work with the clinical reviewers to ensure that clinical information pertinent to the economic review is considered within the clinical review. The economic review is conducted in line with the *Guidelines for the Economic Evaluation of Health Technologies: Canada*. CDA-AMC reviews the cost table provided by the sponsor and critically appraises the sponsor's inputs and assumptions.

CDA-AMC may conduct reanalyses to address the limitations noted with the sponsor's model to provide revised results (i.e., CDA-AMC base-case reanalysis). If reanalyses are not possible, CDA-AMC will comment on the potential impact of such limitations to the economic findings.

The report will include a cost comparison table of the treatments indicated and/or used for the condition in Canada.

9.4. Resubmissions

9.4.1. Target Time Frames

The length of time required to conduct the review of a resubmission or reassessment will be determined based primarily on the following considerations:

- the volume and complexity of the new clinical information to be reviewed
- the complexity of the economic model (e.g., model run time)
- the extent of revisions to the economic model relative to the initial submission (e.g., changes in model structure and/or assumptions)
- the date of filing the application relative to the target meeting date (e.g., filing earlier in the range provides greater opportunities for CDA-AMC to target an earlier expert committee meeting)
- the volume of reviews being conducted concurrently
- whether or not the drug underwent an expedited review by Health Canada.

The sponsor will be notified of the review timelines, including the target expert committee meeting date.

9.4.2. Evidence Review

At the outset of the review, CDA-AMC evaluates the information provided by the sponsor and relevant documents from the initial submission and any previous resubmissions. CDA-AMC determines the appropriate approach to assessing the new information and determines if a new systematic review is

required. In general, the review of a resubmission or reassessment would typically be conducted in accordance with the procedure used for a standard review, though a case-by-case decision is made regarding eligibility for the complex or tailored review processes.

9.5. Standard Reassessment

9.5.1. Target Time Frames

The length of time required to conduct the review of a reassessment will be determined based primarily on the following considerations:

- the volume and complexity of the new clinical information to be reviewed
- the complexity of the economic model (e.g., model run time)
- the extent of revisions to the economic model relative to the initial submission (e.g., changes in model structure and/or assumptions)
- the date of filing the application relative to the target meeting date (e.g., filing earlier in the range provides greater opportunities for CDA-AMC to target an earlier expert committee meeting)
- the volume of reviews being conducted concurrently
- whether or not the drug underwent an expedited review by Health Canada.

The sponsor will be notified of the review timelines, including the target expert committee meeting date.

9.5.2. Evidence Review

At the outset of the review, CDA-AMC evaluates the information provided by the sponsor and relevant documents from the initial submission and any previous resubmissions. CDA-AMC determines the appropriate approach to assessing the new information and determines if a new systematic review is required. In general, the review of a reassessment would typically be conducted in accordance with the procedure used for a standard review, though a case-by-case decision is made regarding eligibility for the complex or tailored review processes.

9.6. Reassessment for a Time-Limited Recommendation

9.6.1. Status Updates Regarding Evidence Generation

CDA-AMC will require status updates from sponsors who have been issued time-limited recommendations. These will consist of brief updates from sponsors regarding the evidence requirements identified in the recommendation and Health Canada Qualifying Notice. To streamline this process for industry, CDA-AMC will align these requests with the format currently described in *Health Canada's Guidance Document: Notice of Compliance with Conditions (NOC/c)* (refer to Appendix 4: Progress of Ongoing Confirmatory Trials Report). An example of the request is provided in Table 19.

Table 19: Status Update Request From CDA-AMC

Category	Sponsor Response
Sponsor	*State company name*
Product	*Brand (non-proprietary name); dosage form and strength*
Project number	*Please add CDA-AMC project number*
Letter of Undertaking Date	*Month Day, Year*
Description of Trial	*Please provide a brief description of the relevant trial*
Trial Schedule	*Protocol approval date; Trial enrollment start date and conclusion date; Last patient evaluation date; Health Canada submission date.*
Current Status	*Pending, Ongoing, Delayed, Terminated, or Submitted*
Explanation of the Status	*Please provide a brief description of the current status.* *Please highlight important protocol amendments.* • *Has the status of the phase III clinical study changed (e.g., ongoing, cancelled, terminated early)?* • *Have the timelines for completing and reporting the phase III study been revised?* • *Have there been amendments to the study protocol that will impact the patient population(s) being studied, outcomes being assessed, dosage or frequency of the drug being administered, and/or revisions to the comparator drug(s).*

CDA-AMC will issue these requests for status updates using standardized forms sent to the sponsor twice per year (at the beginning of April and October). Sponsors will be asked to complete the update within 10 business days and inform CDA-AMC if an extension is required.

Sponsors are also encouraged to proactively inform CDA-AMC regarding any updates to the conduct of the phase III clinical study. To ensure appropriate tracking and triage, please send these updates to CDA-AMC will subsequently contact the sponsor (if required).

This information will be shared with the authorized recipients described within the confidentiality guidelines (refer to Appendix 1) and may be discussed with the CDA-AMC expert committees but will not otherwise be disclosed by CDA-AMC. The expert committees may be asked to evaluate the importance of protocol amendments and their impact on the ability of the phase III study to address the uncertainty with the clinical evidence that was reviewed by the committee (this would be of particular importance in a situation in which the study population, intervention, or outcomes have been revised by the sponsor).

9.6.2. Target Timeframes

9.6.2.1. Filing and Review Timelines

In accordance with the conditions stated within the CDA-AMC recommendation, sponsors of drugs that are issued time-limited recommendations will be required to file for reassessment once the phase III evidence has been generated. Failure to file the required reassessment will mean that the sponsor has not satisfied the conditions of the time-limited recommendation. In these cases, the participating drug programs may file a request for advice, as described in the section on Drug Program–Initiated Reassessment. This may result in CDA-AMC issuing a revised recommendation that the drug should not be reimbursed by the drug programs.

CDA-AMC appreciates that sponsors will require time after the phase III study has been completed to evaluate the clinical data, update the required pharmacoeconomic analyses, and revise the budget impact analysis (as required).

Table 20: Target Timelines for Filing Reassessment Applications

Milestone	Time frame	Description
Formal advance notification of pending reassessment	≥ 30 business days before filing the application	Sponsors must provide formal advance notification to CDA-AMC regarding the pending reassessment application.
Call for input regarding the pending reassessment	29 business days before filing the application	CDA-AMC issues a call for input from interested parties. Notification will be provided that the pending application is for a reassessment of a previously issued recommendation.
Reassessment application filed by sponsor	≤ 270 calendar days[a] after the completion date of the phase III trial[b]	Sponsors must file the reassessment application in accordance with the CDA-AMC requirements. In the event a sponsor fails to file the reassessment application by the deadline, the participating drug programs can file a request for advice and CDA-AMC will determine if the initial time-limited recommendation should be revised.

Milestone	Time frame	Description
Updated draft recommendation issued	≤ 180 calendar days after the reassessment application is accepted for review	CDA-AMC will issue a revised draft recommendation in accordance with the performance metrics stated within the *Fee Schedule for Pharmaceutical Reviews* (i.e., within ≤ 180 calendar days after the reassessment application has been accepted for review). The recommendation will be posted for feedback, and sponsors, or the participating drug programs, will have the opportunity to file a request for reconsideration.

[a] This time frame has been selected to provide industry with sufficient time to prepare the reassessment application and to provide the participating drug programs with a clear time frame for when the time-limited recommendation will be reassessed.

[b] Study completion date: Date final study participant was examined or received an intervention for the final collection of data for the primary and secondary outcome measures and adverse events.

9.6.2.2. Unanticipated Delays With Phase III Study

In the event of an unanticipated delay during the conduct of a phase III clinical trial, CDA-AMC will work with sponsors and the public drug programs on a case-by-case basis to determine if the conditions of the time-limited recommendation can be addressed within an acceptable time frame and, if so, the revised required timelines for the reassessment.

9.6.2.3. CDA-AMC and Health Canada Reviews

The CDA-AMC reassessment process will occur independently of the review by Health Canada (i.e., Supplement to a New Drug Submission – Confirmatory [SNDS-c] review). Although the initial time-limited recommendation process is only for drugs that have received an NOC/c from Health Canada, the CDA-AMC review process will continue to focus on issues related to comparative clinical effectiveness and cost-effectiveness. It is not intended to duplicate Health Canada's review of the new evidence.

The reassessment process for a time-limited recommendation may occur in parallel with the sponsor's submission of an SNDS-c to Health Canada as part of the requirements to address the conditional regulatory approval. In these cases, sponsors are encouraged to participate in the aligned reviews process between Health Canada and CDA-AMC for these SNDS-c applications.

9.6.2.4. Withdrawal of NOC or Cancellation of DIN

If the regulatory review results in withdrawal of the drug and/or indication of interest from the Canadian market, any ongoing reassessment would immediately be stopped in accordance with section 12.5. Any applicable recommendations may be updated with a disclaimer that the drug and/or indication has been withdrawn.

9.6.3. Initiating the Reassessment Process

9.6.3.1. Sponsor-Initiated Reassessment

Eligible sponsors will typically be the Drug Identification Number (DIN) holders for the drug and indication that received the time-limited recommendation from CDA-AMC; however, it could be another manufacturer, supplier, distributor, or other entity that has been recruited by the DIN holder.

9.6.3.2. Drug Program–Initiated Reassessment

The participating drug programs can file a request for advice at any time if there are concerns about changes with the evidence-generation plans that were filed at the time of the CDA-AMC review. This may include, but is not limited to:

- cancellation or postponement of the phase III confirmatory trial;
- amendments to the protocol of the phase III confirmatory trial that could impact the ability of the study to address uncertainty identified by the expert committee;
- failure of the sponsor to file a reassessment application with CDA-AMC.

In these cases, CDA-AMC may determine that the sponsor has not satisfied the terms of the time-limited reimbursement recommendation, and the previous recommendation may be revised. This may include issuing a “do not reimburse” recommendation that will supersede the previous recommendation.

Similar to the existing request for advice process, the manufacturer(s) of the drug(s) (i.e., DIN holder) in question will be apprised regarding the drug program–initiated reassessment and the reasons for the review. The DIN holder will be invited to comment or provide information within 10 business days of receiving the notification from CDA-AMC.

9.6.4. Engagement with Interested Parties

All eligible groups may participate in the reassessment process irrespective of their prior participation with the initial assessment.

9.6.5. Application Requirements for Reassessment

The submission requirements for reassessment of a time-limited recommendation will be the same as those currently described in section 6.

9.6.6. Review Procedure

CDA-AMC will re-review the product with the new evidence and determine if it has addressed the previously identified gaps. The review will be conducted in accordance with the standard reassessment process described in section 9.5.

9.6.7. Recommendation Procedure

9.6.7.1. Placement on Expert Committee Meeting Agenda

The target expert committee meeting for a reassessment will be established based on the target timelines currently used for all applications (refer to the Expert Committee Meeting Schedule).

9.6.7.2. Deliberative Process and Recommendations

The expert committee will deliberate on the new evidence for the reassessment. Outcomes of the reassessment deliberation could include:

- Removal of the time-limited reimbursement condition only: A recommendation that the drug or drug regimen continue to be reimbursed by the participating drug programs in accordance with the reimbursement criteria previously recommended by the CDA-AMC committee (or those criteria that are currently being used by the drug programs at the time of deliberation). In this case, the recommendation will note that the sponsor has satisfied the reassessment requirements, and the time-limited condition will be removed from the recommendation.
- Removal of time-limited reimbursement and revised reimbursement conditions: A recommendation that the drug or drug regimen continue to be reimbursed by the participating drug programs, but with revised reimbursement criteria. In this case, the expert review committee may recommend updated reimbursement conditions to reflect the new evidence and/or advances in the therapeutic space. The recommendation may be updated to reflect the revised pharmacoeconomic economic analysis for the drug or drug regimen. The updated recommendation will note that the sponsor has satisfied the reassessment requirements, and the time-limited condition will be removed from the recommendation.
- The drug or drug regimen should not be reimbursed: This recommendation will be issued if the expert committee concludes that the new evidence is insufficient to address the previously identified uncertainty with the clinical benefit. CDA-AMC could provide implementation advice and/or guidance for a recommendation if requested by the public drug programs.

9.6.7.3. Updated Reimbursement Recommendation

CDA-AMC will issue an updated recommendation that will supersede the previously issued time-limited recommendation. A final recommendation will only be issued after feedback has been provided on a draft recommendation and any requests for reconsideration and/or editorial revisions have been considered and resolved.

9.6.7.4. Request for Reconsideration

Sponsors will be permitted to file a request for reconsideration regarding an updated draft recommendation in the same manner as currently described in section 11.4.

10. Finalizing the Review Report

The draft report and supplemental material are sent to the sponsor for comments and identification of confidential information, and to the drug programs for their information.

10.1. Sponsor Review of Draft Report and Supplemental Material

The sponsor's combined comments on the draft report and supplemental material must be filed using the template and must not exceed the page limitations provided in the instructions. The page limits include any figures, tables, and so forth, but do not include the list of references. The formatting of the template (e.g., page margins, table column widths) must not be altered. If the template filed by the sponsor exceeds the page limits, it will not be accepted. The sponsor will be asked to refile its comments in accordance with the instructions. This could result in the review timelines being delayed, including the drug being considered at a later meeting of the expert committee. If CDA-AMC is prevented from achieving the performance metric because of such a delay, sponsors will not be eligible for a partial refund.

This will be the sponsor's only opportunity to provide comments. The sponsor may waive the opportunity to provide comments by indicating "not applicable" on the comments template. The sponsor's comments should be presented clearly and succinctly in point form, whenever possible. The issue(s) should be clearly stated, and specific reference must be made to the part of the report under discussion. References should be appropriately cited in the comments provided by the sponsor.

In the case of a submission filed on a pre-NOC basis, the report and supplemental material may be revised to reflect the final product monograph or other finalized information provided by the sponsor because of the NOC or NOC/c being granted.

10.1.1. Standard or a Complex Review

The sponsor has 7 business days following receipt of the draft report to review and submit written comments about the report and supplemental material. The following page limits will apply for a standard or complex review:

- A maximum of 10 pages for comments on the draft report and supplemental material (i.e., 10 pages for both documents combined).
- A maximum of 1 additional page for comments on the ethics section of the report (if a separate ethics review is conducted).
- A maximum of 1 additional page for comments on the test procedure assessment section of the report (if a full testing procedure assessment is conducted).

The draft report and supplemental material are revised, as required, based on the sponsor's comments, and are included in the committee brief. The responses to the comments are also incorporated into the

committee brief and are shared with drug programs. The responses to the comments and the revised documents are sent to the sponsor 8 business days prior to the targeted expert committee meeting. The responses and report are provided to the sponsor only for the purposes of identifying confidential information. There are no further opportunities to provide comments on the documents.

10.1.2. Tailored Review

The sponsor has 5 business days following receipt of the draft review report to review and submit written comments about the report. The comments must not exceed 10 pages for a tailored review. The draft review report is revised, as required, based on the sponsor's comments, and are included in the committee brief. The responses and the revised report are sent to the sponsor 8 business days prior to the subcommittee meeting. The responses are provided to the sponsor for information only. The responses are incorporated into the subcommittee brief and are shared with drug programs.

10.2. Identification of Confidential Information

CDA-AMC will post the draft report and supplemental material for all applications. Sponsors are responsible for identifying and requesting the redaction of any confidential information supplied by the sponsor that was used in the preparation of the review report before these documents are posted. CDA-AMC also provides an opportunity for the sponsor to review the feedback from the drug programs on the draft recommendation to ensure that it does not contain any confidential information. This is offered, as the drug programs may consider the unredacted draft recommendation when providing their input.

Content identified as confidential information is expected to be kept to a minimum. It is not acceptable to mark an entire paragraph or section as confidential.

CDA-AMC will post the draft review report and supplemental material at the same time as the draft recommendation. The sponsor will receive the revised report and supplemental material 8 business days before the expert committee meeting or subcommittee meeting. The sponsor will then have 8 business days to identify confidential information in the draft review report and supplemental material. This will be the sponsor's only opportunity to request redactions from the draft review report and supplemental material. The sponsor must submit the redaction request form to CDA-AMC using the Pharmaceutical Review SharePoint Site within 8 business days.

Sponsors must identify any confidential information in the draft report by providing:

- a completed identification of confidential information form
- a copy of the review report with confidential information highlighted in yellow.
- A copy of supplemental material with confidential information highlighted in yellow.

The sponsor may waive the opportunity to request redactions by indicating "not applicable" on the identification of confidential information form or by confirming via email.

CDA-AMC will redact confidential information (as required) within 6 business days. The sponsor will then receive the redacted review report and supplemental material and will have 4 business days to validate that all confidential information has been redacted. If revisions to redactions are needed, the sponsor will receive an updated redacted draft review report and supplemental material at the same time as the draft recommendation.

Table 21: Time Allotted for Redaction of Review Report and Supplemental Material

Key milestone	Description and timing	Business days
Sponsor receives draft report and supplemental material	Sponsor will receive the revised report and supplemental material 8 business days before the expert committee meeting or subcommittee meeting.	0
Sponsor identifies redactions	The sponsor has 8 business days to submit the identification of confidential information form to request redactions.	8
Redactions	Confidential information is redacted in accordance with the *Reimbursement Review Confidentiality Guidelines*.	6[a]
Sponsor verifies redactions	Sponsors are sent the final redacted and unredacted documents to review and confirm the redactions.	4

[a] This is a target of 6 business days. Extensions may be required depending on the nature, complexity, and clarity of the redaction requests.

11. Recommendation Procedure

11.1. Committee Meetings

11.1.1. Meeting Preparation

11.1.1.1. Meeting Agenda

The expert committee meeting agenda is set by CDA-AMC and the committee chair. Applications that satisfy the preliminary eligibility criteria for a time-limited recommendation (i.e., based on regulatory review pathway and timelines for evidence generation) will only be placed on the agenda when the information noted in the qualifying notice has been provided to CDA-AMC and relevant information incorporated into the report and recommendation.

11.1.1.2. Committee Briefing Materials

CDA-AMC compiles and distributes the committee brief to all members of the expert committees and the drug programs 10 business days before the next scheduled meeting. The committee members are responsible for reviewing the briefing materials for all drugs under consideration at the meeting. Materials contained in the committee brief for each drug under review include, but are not limited to the following:

- patient group input

- clinician group input
- drug program input
- clinical and economic review report
- sponsor's comments on the draft report and the review team's responses
- reimbursement status for the drug under review and its relevant comparators
- a summary of all recommendations issued with the same or a similar indication as the drug under review
- a summary of regulatory decisions and HTA recommendations for the drug under review in other jurisdictions
- additional information, such as reference material (for review report[s]) or sponsor-provided executive summary and table of studies.

In addition to the materials in the committee brief, the committee has access to the complete package of requirements filed by the sponsor. Therapeutic review and optimal use reports may be included in the committee briefing materials when available and relevant.

11.1.2. Meeting Minutes

Minutes of committee deliberations will be taken so that there is a record of attendance at the meeting, of the recommendations made, and of the decisions and actions.

11.1.3. Attendance

In addition to the expert committee members, the following people may attend a committee meeting in accordance with the terms of reference for the expert committees:

- Health ministry officials appointed by participating jurisdictions may attend as observers and may contribute information on practical considerations as described in the decision-making framework, but do not have the right to vote.
- Representatives of the pCPA office may attend as observers and may ask clarification questions as needed, but do not have the right to vote.
- Relevant CDA-AMC staff and external reviewers contracted by CDA-AMC may actively participate in the presentation of information. The staff role includes provision of administrative and secretariat support. CDA-AMC staff and external reviewers do not have the right to vote.
- External experts (including clinical specialists) attend the expert committee meetings upon invitation from CDA-AMC. These clinical experts provide input regarding the drug under review, address questions from the committee, and may assist in establishing and refining reimbursement conditions. They do not vote on the recommendation.

- Persons with lived experience and/or patient group representatives may attend meetings to provide their perspective for some complex reviews. They do not vote on the recommendation.

Sponsors, patients, and others (except as previously described) are not entitled to attend any expert committee meeting, either as observers or to make an oral presentation or submission.

11.1.4. Deliberative Process

At the committee meeting, expert committee members consider and discuss each committee brief on the meeting's agenda to make a recommendation. Consideration of each submission or resubmission begins with presentations by the CDA-AMC review team and each of the assigned lead presenters (as well as the person with lived experience if applicable) as follows:

- If a person with experience with the condition under review has been engaged by CDA-AMC, the person delivers a brief presentation and answers questions from the expert committee.
- The CDA-AMC review team summarizes the evidence included in the review and the CDA-AMC critical appraisal of the clinical and economic evidence and answers questions from the expert committee.
- The assigned patient member presents the perspectives and issues of patients and/or their caregivers related to the condition for which the drug under review is indicated, the impact and unmet needs of current therapy, the treatment outcomes of greatest importance, and the expectations for the drug under review, as identified in the input submitted by patient groups.
- The 1 to 2 assigned technical presenters present their assessment of clinical and pharmacoeconomic evidence.
- If there is a separate ethics review, the CDA-AMC review team summarizes the identified ethics and equity considerations, and the ethicist member presents an overview of considerations raised and their relevance to the assessment of the drug under review.

Following the presentations, all expert committee members provide input. The review team and invited external experts provide input as required. The assigned leads' presentations and the expert committee's deliberation are informed by the materials in the committee brief.

11.1.5. Drafting Recommendations

The committee must make a recommendation or defer if additional clarification is needed.

11.1.5.1. Submissions and Resubmissions

Based on the deliberation of the available evidence, the committee members choose one of the recommendation options described in section 11.3.2, provide reasons for the recommendation, and implementation guidance (when applicable). The reasons for the recommendation will represent the key considerations and rationale used by the committee in formulating the recommendation. CDA-AMC staff

may be tasked with preparing the draft reasons for the recommendation, for approval by the committee members.

11.1.5.2. Reassessments

The committee may address reassessments by one of the following approaches:

- providing a revised recommendation that would supersede a previous final recommendation (e.g., changes to the recommendation category and/or reimbursement conditions)
- upholding the existing recommendation and providing additional context and/or clarifications that address the reassessment in an updated recommendation document.

In both scenarios noted above, a draft recommendation will be released (as described in section 11.4). The recommendation document would include standardized disclaimers that indicate that the new recommendation supersedes the previous recommendation that was issued at the conclusion of the initial review of the drug.

11.1.6. Voting on Recommendations

The committee members vote on the recommendation in the following manner.

- Only committee members may vote.
- All members must vote unless there is a declared conflict of interest that precludes a member from voting.
- The committee members will vote anonymously on the recommendation.
- The reasons for the recommendation are drafted and discussed before committee members vote on a recommendation.
- The committee chair validates the voting results and announces if the motion is carried. Results of the vote are determined based upon a simple majority of the voting members.
- The committee chair votes only in the case of a split vote.

11.1.7. Deferring a Recommendation

If the committee needs additional information from CDA-AMC, sponsor, or external experts, the matter will be deferred to a subsequent meeting of the expert committee, pending the collection of such information.

11.2. Subcommittee Meetings

11.2.1. Meeting Preparation

CDA-AMC compiles and distributes the subcommittee brief to the members and drug programs 10 business days before the meeting. The subcommittee members are responsible for reviewing the briefing materials for all drugs under consideration at the meeting. The materials contained in the subcommittee brief for each drug under review will be similar to those described in section 11.1.1.2.

11.2.2. Meeting Minutes

Minutes of committee deliberations will be taken so there is a record of attendance at the meeting, the recommendations made, and the decisions and actions.

11.2.3. Subcommittee Composition

CDA-AMC will convene a subcommittee of members from the relevant expert committee (i.e., CDEC for non-oncology drugs and pERC for oncology drugs) to conduct the deliberation and issue the recommendation for tailored review applications. The subcommittee will typically be composed of the chair (or vice-chair in their absence), 2 assigned technical lead presenters, and a patient member. If there is a conflict of interest relevant to the review that precludes a member from voting, they will not be included in the subcommittee.

11.2.4. Attendance

The attendees at the subcommittee meeting will generally be similar to those permitted to attend the full committee meetings (section 11.1.2). As with the full committee meetings, the deliberations will be supported by external clinical specialists with expertise in the diagnosis and management of the condition for which the drug under review is indicated. These clinical experts provide input regarding the drug under review and address questions from the committee. They do not vote on the recommendation. As with the full committee meetings, public drug programs may attend the subcommittee meetings and may be asked to comment on potential implementation issues for the drug under review.

Sponsors, patients, and others (except as previously described) are not entitled to attend any the subcommittee meeting, either as observers or to make an oral presentation or submission.

11.2.5. Deliberative Process

The subcommittee must make a recommendation or defer the deliberation. Consideration of the application begins with each of the assigned lead presenter(s) as follows:

- The assigned patient member presents the perspectives and issues of patients and/or their caregivers related to the condition for which the drug under review is indicated, the impact and

unmet needs of current therapy, the treatment outcomes of greatest importance, and the expectations for the drug under review, as identified in the input submitted by patient groups. This information provides context for deliberating the clinical and economic evidence.

- The assigned technical presenter(s) share their assessment of the clinical and pharmacoeconomic evidence.

The subcommittee will then focus its deliberations on the following issues:

- Does the evidence support that the drug under review demonstrates a comparable clinical benefit and harms to 1 or more appropriate comparators?
- Does the evidence support that the drug should be reimbursed in accordance with the existing reimbursement criteria for the most appropriate comparator(s)?

11.2.6. Drafting Recommendations

For a tailored review, a recommendation in favour of reimbursement will typically include the following:

- conditions that the initiation, renewal, and discontinuation criteria should align with those previously recommended and/or currently being used by the drug programs
- a pricing condition that the total cost of the drug under review should not exceed the total cost of the appropriate comparators.

It is important that sponsors note that the appropriate comparators for a pricing condition will not necessarily be limited to those reflected in the indirect comparison filed by the sponsor. As stated in section 5.1.3, for a PACES submission, CDA-AMC may be willing to accept an application in which the comparative clinical data are focused on a more restricted list of relevant comparators, but this does not mean the excluded comparators will not be considered relevant for the purposes of establishing a pricing condition in the recommendation.

As with drugs considered by the full expert committee, the reasons for the recommendation will represent the key considerations and rationale used by the committee in formulating the recommendation. CDA-AMC staff may be tasked with preparing the draft reasons for the recommendation, for approval by the committee members.

11.2.7. Voting on Recommendations

The subcommittee members vote on the recommendation in the following manner:

- Only the committee members may vote.
- All members, excluding the meeting chair, must vote.
- The reasons for the recommendation are drafted and discussed before committee members vote on a recommendation.

- The meeting chair validates the voting results and announces if the motion is carried (i.e., all members voted in favour of the recommendation).

11.2.8. Deferring a Recommendation

If the subcommittee needs additional information from the sponsor, CDA-AMC, or external experts, the matter may be deferred to a subsequent meeting of the subcommittee, pending the collection of such information. In exceptional circumstances, the committee chair may choose to defer the deliberations on the drug under review to the full expert committee rather than the subcommittee (e.g., in the event there is a lack of consensus).

11.2.9. Reconsideration

If a sponsor files a request for reconsideration based on major revisions (e.g., following a do not reimburse recommendation from the subcommittee), the reconsideration deliberations will occur with the full expert committee. In the event the sponsor files a request for reconsideration based on minor revisions, CDA-AMC would reconvene the subcommittee to address the reconsideration.

11.3. Deliberative Framework and Recommendation Framework

11.3.1. Deliberative Framework

The expert committee and subcommittee deliberations are guided by the deliberative framework in the Expert Committee Deliberation at Canada's Drug Agency document. The deliberative framework consists of 5 domains of value that are relevant for the expert committee to consider in their deliberations: clinical value, unmet clinical need, distinct social and ethical considerations, economic considerations, and impacts on health systems.

11.3.2. Recommendation Framework

11.3.2.1. Recommendation Options

The expert committees may recommend 1 of the following options for a drug under review: that a drug be reimbursed, that a drug be reimbursed with conditions, that a drug be reimbursed in a manner that is time-limited and subject to a future reassessment, or that a drug not be reimbursed (Table 22). Please note that the scenarios described within Table 22 are meant to be illustrative and are not exhaustive.

Table 22: Description of Recommendations

Category	Description
Reimburse	The drug under review demonstrates comparable or added clinical benefit and acceptable cost or cost-effectiveness relative to one or more appropriate comparators[a] to recommend reimbursement in accordance with the defined patient population under review, which is typically the patient population defined in the Health Canada–approved indication (as applicable).
Reimburse with conditions	Scenarios that could be considered under this category include: • The drug under review demonstrates comparable or added clinical benefit and acceptable cost or cost-effectiveness relative to one or more appropriate comparators in a subgroup of patients within the approved indication. In such cases, conditions are specified to identify the subgroup. • The drug under review demonstrates comparable clinical benefit and acceptable cost or cost-effectiveness relative to one or more appropriate comparators.[a] In such cases, a condition may include that the drug be listed in a similar manner to one or more appropriate comparators.[a] • The drug under review demonstrates comparable or added clinical benefit, but the cost or cost-effectiveness relative to one or more appropriate comparators[a] is unacceptable. In such cases, a condition may include a reduced price. • The drug under review demonstrates clinical benefit, with a greater degree of uncertainty and an acceptable balance between benefits and harms in a therapeutic area with significant unmet clinical need. In such cases, if the cost or cost-effectiveness relative to one or more appropriate comparators[a] is unacceptable, a condition may include a reduced price.
Time-limited reimbursement	The evidence-generation plans described in Health Canada's qualifying notice are expected to address the gaps in the evidence identified by the expert committee.
Do not reimburse	There is insufficient evidence identified to recommend reimbursement. Scenarios that typically fit this recommendation category include: • The drug under review does not demonstrate comparable clinical benefit relative to one or more appropriate comparators.[a] • The drug under review demonstrates inferior clinical outcomes or significant clinical harm relative to one or more appropriate comparators.[a]

Notes: The scenarios described in this table are meant to be illustrative and are not exhaustive.

Existing treatment options may include best supportive care and nonpharmaceutical health technologies or procedures.

[a] An appropriate comparator is typically a drug reimbursed by 1 or more drug programs for the indication under review. However, the choice of appropriate comparator(s) in the review is made on a case-by-case basis, considering input from jurisdictions and clinical experts.

11.3.2.2. Reimbursement Conditions

The expert committee may specify that a recommendation in favour of reimbursement is contingent upon one or more conditions being satisfied. These conditions commonly include initiation criteria, renewal criteria, discontinuation criteria, prescribing criteria, and conditions related to the price of the drug.

Table 23 provides some examples of conditions that are commonly included in reimbursement recommendations. The examples cited are intended to serve as illustrations only to help guide the reader to better understand some of the factors that the expert committees will assess as part of their deliberations in formulating a reimbursement recommendation and are by no means exhaustive or impose any procedural obligations that would constitute grounds for a procedural review.

Table 23: Examples of Commonly Used Reimbursement Conditions

Reimbursement conditions	Description
Initiation criteria	Provides guidance on the appropriate reimbursement criteria for initiating treatment with the drug under review. Commonly used patient characteristics include: • severity of the condition • treatment history (e.g., inability to use, intolerance, or inadequate response to appropriate comparator[s]) • comorbidities • subtypes of the condition (e.g., based on genotypic and/or phenotypic characteristics).
Renewal criteria	Provides guidance on how and when patients who are receiving the drug should be assessed to determine if they are benefiting from the treatment. Commonly used criteria include: • minimum treatment response for continuation of therapy • type and timing of the clinical assessment(s) that should be used to evaluate the response to treatment.
Discontinuation criteria	Provides guidance on when reimbursement of the drug under review should be discontinued. These conditions can be used to identify the drug in patients who are longer responding and/or benefiting from treatment. Commonly used criteria include: • need for an invasive intervention (e.g., organ transplant or ventilation) • initiation of a different therapy for the condition • disease progression.
Prescribing criteria	Provides guidance on the appropriate setting for the treatment. Commonly used criteria include: • that prescribing and/or administration should be limited to clinicians or health care teams with a particular area of expertise • restrictions on dosage strength and frequency of administration • restrictions on combination use with other drugs.
Pricing conditions	Provides guidance on cost considerations for the drug under review. Commonly used criteria include: • a reduction in price (i.e., cost-effectiveness must be improved)

Reimbursement conditions	Description
	• that the cost of the drug under review does not exceed the cost of appropriate comparator(s) • that the cost of the drug under review should provide cost savings compared with appropriate comparator(s).
Feasibility of Adoption into the Health System	Provides an assessment of the ease with which the drug can be adopted into the overall health care and cancer care systems. Feasibility of adoption may be noted in the following scenarios: • Economic feasibility may be noted when there are concerns regarding the affordability of the drug under review based on the budget impact assessment. • Organizational feasibility may be noted when there are concerns regarding the ability of the health system to adopt the drug under review based on an assessment of health system enablers and barriers to implementation, as identified by the participating drug programs, inclusive of all elements: operational, capital, human resources, legislative, and regulatory requirements.
Time-limited reimbursement	A recommendation in favour of reimbursement is time-limited and contingent on a future reassessment of additional evidence that addresses the uncertainty. The expert committee will describe the key limitations of the clinical evidence that must be addressed through the completion of the pending phase III study being conducted by the sponsor.

11.3.2.3. Considerations for Significant Unmet Need

In exceptional cases where there is uncertain clinical and pharmacoeconomic evidence, the expert committees may issue a recommendation to reimburse with conditions, due to practical challenges in conducting robust clinical trials and pharmacoeconomic evaluations and in the presence of significant unmet medical need. In these situations, although there is uncertainty with the clinical evidence, the available evidence must reasonably suggest that the drug under review could substantially reduce morbidity and/or mortality associated with the disease. Significant unmet clinical need is identified on a population or subpopulation basis (i.e., not on an individual basis) through CDA-AMC's drug review processes.

Please note that the scenario examples noted in Table 24 are intended to serve as illustrations only to help guide the reader to better understand some of the factors that expert committees will assess as part of their deliberation in formulating a reimbursement recommendation, and are by no means exhaustive or impose any procedural obligations that would constitute grounds for a procedural review.

Please also note that the rarity of the condition will not be the sole consideration for defining significant unmet need. The condition must also be identifiable with reasonable diagnostic precision.

Table 24: Considerations for Significant Unmet Need and Uncertainty of Clinical Benefit

Consideration	Description
Considerations for significant unmet need	
Rarity of condition	• The drug under review is approved by Health Canada for the treatment of a rare disease. Specifically, the condition for which the drug is indicated has the following characteristics: ○ is life-threatening, seriously debilitating, or both serious and chronic in nature. ○ affects a relatively small number of patients (incidence of fewer than 5 in 10,000, but typically closer to 1 in 100,000) ○ is often genetically based, onset at birth or early childhood, and leads to a shortened lifespan ○ places a heavy burden on caregivers and the health care system ○ is difficult to study because of the small patient population.
Population	• Need is identified on a population or subpopulation basis and not on an individual basis.
Absence of alternatives	• There is an absence of clinically effective drug or non-drug alternative treatments. • Substantial morbidity and mortality exist despite the available drug or non-drug alternative treatments.
Factors that contribute to uncertainty of clinical benefit	
Clinical data	• Limited number of clinical studies • Small sample sizes (e.g., due to rare disease that affects a relatively small number of patients [incidence of fewer than 5 in 10,000, but typically closer to 1 in 100,000]) • Absence of comparator groups • Alternative or adaptive trial designs for rare diseases • Short study durations or follow-up • Inability to distinguish disease severity in heterogeneous manifested rare diseases • Limited to surrogate end points • Insufficient evidence on meaningful clinical end points • Greater uncertainty in statistical analyses

11.3.2.4. Time-Limited Reimbursement Recommendations

For applications that may receive a time-limited recommendation, the committee will be provided with the evidence-generation plans specified within the qualifying notice for consideration during the deliberations. The committee will consider a time-limited recommendation, but may issue an alternative recommendation as currently described in 11.3.2.1 (i.e., reimburse, reimburse with conditions [without a time-limited condition], or do not reimburse).

In accordance with the recommendation framework, to receive a recommendation in favour of reimbursement when there is uncertainty with the clinical evidence at the time of the review, the available evidence must reasonably suggest that the drug under review could substantially reduce morbidity and/or mortality associated with the disease versus comparators identified within the review. In situations

where the gaps in the evidence identified by the expert committee align with those identified in the qualifying notice for the NOC/c, the committee may issue a time-limited recommendation.

If the expert committee identifies additional important gaps in the clinical evidence that are outside the scope of the phase III clinical trial described within the Qualifying Notice, this may result in a recommendation that the drug is not reimbursed or a recommendation that the drug be reimbursed only for subset of the population where there is sufficient evidence to draw conclusions regarding the comparative clinical benefit (with or without a time-limited reimbursement condition).

The recommendation document will state that the reimbursement recommendation is being issued in a manner that is time-limited and contingent on further evidence generation to address the uncertainty in the evidence. CDA-AMC will provide notification that the recommendation is time-limited by including the following:

- **Recommendation category:** The recommendation category will state “time-limited recommendation” on the CDA-AMC website and on the cover page of the recommendation document.
- **Cover page:** The cover page of the recommendation document will note that the category of decision is a “time-limited recommendation.” In addition, the following statement will be included on the cover page: This recommendation is time-limited and contingent on a future reassessment of additional evidence that addresses the uncertainty.
- **Recommendation statement**: The reimbursement recommendation statements will be structured in the following format: The expert committee recommends that [DRUG] be reimbursed for the treatment of [INDICATION] for a time-limited period while additional evidence is generated…
- **Reimbursement condition:** The table of reimbursement conditions will include an additional category for “time-limited reimbursement.” The condition will state: The recommendation in favour of reimbursement is time-limited and contingent on a future reassessment of additional evidence that addresses the uncertainty.
- **Reason for condition:** The reason for the time-limited reimbursement condition will be stated. The expert committee will describe the key factors that contribute to uncertainty with the clinical evidence that must be addressed through the completion of the pending phase III study being conducted by the sponsor.
- **Implementation guidance:** The expert committees will note in the recommendation the anticipated timelines for completion of the required study. Implementation guidance will typically reflect the issues identified within the clinical review report, but the committee may raise additional issues that arise during the deliberations. Interested parties would have the opportunity to review and provide feedback on these issues within the draft recommendation documents.

An example of how the time-limited reimbursement condition will be presented within the recommendation is provided in Table 25.

Table 25: Sample Time-Limited Reimbursement Condition

Reimbursement condition	Reason	Implementation guidance
Time-limited reimbursement		
A recommendation in favour of reimbursement is time-limited and contingent on a future reassessment of additional evidence that addresses the uncertainty.	The expert committee will describe the key limitations of the clinical evidence that must be addressed through the completion of the pending phase III study being conducted by the sponsor.	The expert committee will note the anticipated timelines for completion of the required study.

11.4. Draft Recommendations

11.4.1. Issuing a Draft Recommendation

In the case of a submission that was filed on a pre-NOC basis, the draft recommendation will not be released until CDA-AMC has received a copy of all the required information, including a copy of the NOC or NOC/c. CDA-AMC will review the information and determine if the draft recommendation will be issued or if the drug should be placed on the agenda of a subsequent meeting of the expert committee. The sponsor will be notified of any revisions to the anticipated timelines.

The draft recommendation will be sent to the sponsor and drug programs 8 to 10 business days following the expert committee meeting at which the recommendation was made. Time-limited recommendations will be issued in the same manner as other reimbursement recommendations.

Before a recommendation is posted, sponsors are responsible for identifying and requesting the redaction of any confidential information supplied by the sponsor that has been included in the draft recommendation. Confidential information will be redacted in accordance with the Reimbursement Review Confidentiality Guidelines. Pursuant to the Reimbursement Review Confidentiality Guidelines, CDA-AMC will indicate that confidential information was used to make the reimbursement recommendation, and that the sponsor requested that this information be kept confidential.

Sponsors are asked to identify any confidential information in the draft recommendation using the identification of confidential information template. All requests for redactions must be accompanied by a clearly stated rationale. Sponsors must submit the completed form via the “5. CDA-AMC Review Reports and Recommendations” folder on the Pharmaceutical Submissions SharePoint site by the date and time specified in the notice of the draft recommendation (typically 4:00 p.m. Eastern Time 2 business days after the draft recommendation was issued to the sponsor and drug programs).

If the sponsor expresses disagreement regarding redactions made in the draft recommendation, additional time may be required to resolve the disagreement in consultation with the sponsor. This additional time could delay the timeline for posting the draft recommendation.

Table 26: Target Timelines for Issuing and Posting Draft Recommendations

Key milestones	Description
Issuance to sponsor and drug programs	Draft recommendation issued 8 to 10 business days after the expert review committee meeting
Sponsor identifies confidential information	Sponsor has 2 business days to identify any confidential information in the draft recommendation using the template
Redaction of confidential information	Confidential information redacted 1 business day after receipt of the completed template from the sponsor
Sponsor validates redactions	Sponsor has 1 business day to validate the redactions in the recommendation after receipt from CDA-AMC
Posting on CDA-AMC's website	The draft recommendation will be posted on the day of the next scheduled issuance of Weekly Summary
Feedback period	The feedback period will be 10 business days after the draft recommendation is posted on the website

11.4.2. Feedback on a Draft Recommendation

All draft recommendations are posted for feedback, and the feedback period begins when the draft recommendation is posted on the CDA-AMC website. The intent of the feedback period is to allow time for the sponsor, drug programs, and other eligible parties to comment on the draft recommendation and provide feedback before it is finalized and posted. The draft report and supplemental material are posted at the same time as the draft recommendation for information only and are not subject to feedback.

The sponsor, the manufacturer of the drug under review (if not the sponsor), the drug programs, patient groups, and clinician group(s) may provide feedback on the draft recommendation. Interested parties will have 10 business days to review the draft recommendation and provide feedback (the day the recommendation is posted is considered day zero). Sponsors, patient groups, and clinician groups must provide feedback using the template; feedback must be disclosable and will be posted on the website. Feedback from the drug programs is provided using a dedicated feedback form. Prior to posting, sponsors are given the opportunity to review the feedback from the drug programs to ensure that it does not contain any confidential information. This is offered as an additional measure in the event the drug programs have considered confidential information within the unredacted draft recommendation when providing their input.

During the feedback period, the sponsor and/or the drug programs may make a request for reconsideration (section 11.5).

Table 27: Groups Eligible to Provide Feedback on Draft Recommendations

Source	Scope of feedback
Sponsor	• Provide feedback on the draft recommendation • File a request for reconsideration of the draft recommendation
Manufacturer (if not the sponsor)	• Provide feedback on the draft recommendation
Drug programs	• Provide feedback on the draft recommendation • File a request for reconsideration of the draft recommendation
Patient group(s)	• Provide feedback on the draft recommendation
Clinician group(s)	• Provide feedback on the draft recommendation

11.5. Request for Reconsideration

11.5.1. Eligibility

The sponsor of a drug that is the subject of a draft recommendation and the drug programs may file a request for reconsideration of the recommendation during the feedback period. The sponsor and drug programs are entitled to have the draft recommendation reconsidered one time (this does not include situations where a revised draft recommendation has been issued after a request for reconsideration).

A request for reconsideration can be made only on the grounds that the recommendation is not supported by the evidence that has been submitted or the evidence identified in the review report. A request for reconsideration cannot be made solely because the sponsor or drug programs disagree with the recommendation. The request for reconsideration must identify the aspect(s) of the draft recommendation with which the sponsor or drug programs disagree.

The sponsor and drug programs may only file a request for reconsideration during the feedback period. CDA-AMC provides notification of the reconsideration on the project webpage.

Sponsors will be permitted to file a request for reconsideration regarding time-limited recommendations in the same manner as other recommendations. Reconsiderations requesting the removal or modification of condition(s) specifying that the recommendation is time-limited and contingent on evidence generation and reassessment will typically be managed in accordance with the processes for requests based on major revisions.

11.5.2. Reconsideration Options

As shown in Table 28, reconsideration requests are stratified depending on the focus, complexity, and effort required to address the request. There are 3 categories:

- Major revisions: Requests for major revisions will typically be focused on the recommendation category (e.g., do not reimburse) or involve revisions that would result in changes to the patient

population that would be eligible for reimbursement with the drug under review (e.g., expansion of the patient population addressed in the initiation criteria).

- Minor revisions: Requests for minor revisions will typically be focused on any of the following: reimbursement conditions within the patient population for whom reimbursement of the drug under review has been recommended (e.g., renewal criteria or administration criteria); implementation guidance; or reasons for recommendation. Requests for minor revisions that would alter the patient population (e.g., expanding the population or the criteria related to the identification of appropriate patients) will not be accepted and the request will have to be refiled as a request for major revisions.
- Editorial revisions: Requests to revise the text in the recommendation to provide additional clarity and details regarding the recommendation, evidence that was considered, the deliberative process, or reasons for recommendation.

These categories have been developed to provide additional flexibility before the recommendation is finalized.

Table 28: Reconsideration Options

	Major revisions	Minor revisions	Editorial revisions
Criteria	Reconsideration requests that are focused on the recommendation category (e.g., do not reimburse); or requests that would result in changes to the patient population that would be eligible for reimbursement with the drug under review (e.g., expansion of the patient population address in the initiation criteria).	Reconsideration requests that are focused on any of the following: reimbursement conditions within the patient population for whom reimbursement of the drug under review has been recommended (e.g., renewal criteria or administration criteria); implementation guidance; or reasons for recommendation.	Requests to revise the text in the recommendation to provide additional clarity and details regarding the recommendation, evidence that was considered, the deliberative process, or reasons for recommendation.
Deliberation	All requests for major revisions to the recommendation will be addressed through discussion and deliberation with the full expert committee with additional support from clinical experts.	The majority of requests for minor revisions will be addressed through discussion and deliberation with a subpanel of the expert review committee with additional support from clinical experts, as required.	CDA-AMC staff and the expert committee chair will address the majority of requests for editorial revisions. Other committee members may be consulted, as required.

	Major revisions	Minor revisions	Editorial revisions
Outcomes	Should the recommendation be substantially revised following deliberation on the reconsideration request, another draft recommendation for feedback. A final recommendation will be issued if the committee upheld the existing recommendation or made only minor revisions to the recommendation.	To expedite the review timelines, another draft recommendation is not issued following deliberations on a request for minor revisions. A final recommendation will be issued whether the committee decided to uphold the existing recommendation or make minor revisions to the recommendation.	These will be limited to editorial revisions or corrections that do not impact the reimbursement recommendation.
Timelines	Requests for major revisions to a recommendation will typically require 2 to 3 months to address.	Requests for minor revisions to a recommendation will typically require 1 month to address.	A final recommendation will be issued in accordance with standard timelines (i.e., typically no delays).
Eligibility	Due the resources required to address these requests and the implications for timelines, only those directly involved in the negotiations for the drug under review are permitted to file these requests (i.e., the sponsor and the drug programs).		All groups who are eligible to provide feedback on reimbursement recommendations may request editorial revisions.
Patient and clinician groups	The committee will consider feedback on the recommendation from clinicians and patient groups in the deliberations for the reconsideration request.		Patient and clinician groups may request editorial revisions.
Fee schedule	Requests filed by sponsors will be subject to a schedule D application fee.		Not applicable.

11.5.3. Filing a Request for Reconsideration

11.5.3.1. Request for Major or Minor Revisions

A request for major or minor revisions is filed by the sponsor using the reconsideration request template and by the drug programs using a dedicated feedback form. The completed template must be received by CDA-AMC during the feedback period.

11.5.3.2. Request for Editorial Revisions

Requests for editorial revisions may be filed by any eligible group using the feedback template. Editorial revisions should not be filed using the request for reconsideration template.

11.5.4. Patient and Clinician Group Feedback

Reconsiderations result in a significant extension of the overall review timelines (typically 2 to 3 months) and have important resource implications for CDA-AMC, as well as for sponsors. As such, only those directly involved in the negotiations for the drug under review are permitted to file requests for reconsideration (i.e., the sponsor and the drug programs). This helps provide greater predictability in the review timelines for sponsors, minimize the overall review timelines for decision-makers and patients, and helps to avoid delays to accessing new medications.

Clinician groups and patient groups still play an important role in the reconsideration process as their feedback on the draft recommendation will be considered by the committee members in their deliberations for the reconsideration request.

11.5.5. Examination of Request for Reconsideration

11.5.5.1. Assessment and Timelines

CDA-AMC will examine, within 5 business days, each request for reconsideration to determine whether the issue(s) raised can be resolved in discussions with the sponsor and/or drug programs. It may be that the issue(s) can be clarified, and the sponsor will accept the recommendation. To minimize the overall timelines for the review, CDA-AMC aims to resolve requests for reconsideration in the most efficient manner. In some cases, requests for reconsideration may be resolved through editorial revisions to the recommendation document. In such cases, CDA-AMC may contact the sponsor and/or drug programs for confirmation that the editorial revisions are acceptable, and that the reconsideration process will not be required to resolve the issues.

If CDA-AMC is unable to address the issue(s), the request for reconsideration is accepted and will be forwarded to the expert committee. When a request for reconsideration is accepted, the sponsor is offered an optional 1-hour meeting with CDA-AMC to ensure clarity around the key issues raised in their request for reconsideration so that these can be clearly presented by CDA-AMC to the expert committee members. In the event the request for reconsideration is not accepted, CDA-AMC will finalize and issue the recommendation in accordance with section 11.6. The recommendation will be typically issued 5 business days after the decision not to accept the request for reconsideration has been communicated to the sponsor.

Requests for reconsideration that are focused on the rationale for the pricing condition(s) that have been included in the recommendation (e.g., reasons noting a particular reduction in price could be required for the drug under review to be considered cost-effective relative to an appropriate comparator) will not be accepted. CDA-AMC will not accept these requests for reconsideration as they are related to the findings of the CDA-AMC economic report as opposed to the committee's recommendation. As stated in section 11.5.1, a request for reconsideration can be made only on the grounds that the recommendation is not supported by the evidence that has been submitted or the evidence identified in the review report. A request for reconsideration cannot be made solely because a sponsor or the participating drug programs disagree with the recommendation.

When the draft recommendation is issued, sponsors have already been provided with an opportunity to review and comment on the economic report. The feedback period and reconsideration process are not intended to provide additional opportunities for the sponsor to comment on issues that have been or should have been highlighted in the sponsor's comments on the draft report. The sponsor's comments on the draft economic report are provided to the expert committee members. The refiling of commentary on the economic report through the request for reconsideration process is not an efficient use of resources and the requests will not be accepted.

11.5.5.2. New Information

CDA-AMC may allow sponsors to provide new information during the reconsideration process in selected circumstances. The decision to allow new information during the reconsideration will be made solely by CDA-AMC based on the following considerations:

- the application was accepted through the complex review process
- the new information has been provided to try and address an important clear gap in the evidence that has been identified by the expert committee
- the sponsor confirms in writing that the new information was not available during the review phase of the reimbursement review process (i.e., it could not have been included in the initial application without substantially delaying the overall review process and was not available at the time of providing comments on the draft report)
- the expert committee has concluded that the drug under review has the potential to address an important unmet medical need
- the drug under review was reviewed by Health Canada through an expedited review pathway (e.g., priority review)
- the sponsor provides the new information in a format that allows a detailed review and appraisal of the data (e.g., in accordance with the CONSORT reporting guidelines).

As the inclusion of new information during the reconsideration process cannot reasonably be anticipated by CDA-AMC, the timelines for managing these situations will be established on a case-by-case basis. Any sponsors who feel they have new information that may address an important gap in the evidence that has been identified by the expert committee should identify the new information within the reconsideration request template when submitting the request.

11.5.6. Timelines for Expert Committee Meeting

The sponsor will be notified regarding the target expert committee meeting date for the reconsideration. The following factors are considered when establishing the timelines for reviewing a request for reconsideration:

- the grounds and complexity of the request for reconsideration

- the time required to examine the grounds for the request and determine whether the request will be accepted (e.g., depending on the complexity of the request this can take up to 5 business days)
- whether or not the sponsor would like to participate in the 1-hour meeting offered to discuss the request for reconsideration
- the time required to prepare documentation from the reconsideration meeting for inclusion in the committee brief (e.g., meeting minutes)
- the deadline for the reconsideration committee brief to be delivered to all members and the drug programs (i.e., typically at least 10 business days before the scheduled expert committee meeting).

11.5.7. Reconsideration Meeting

CDA-AMC offers a meeting in situations where the sponsor has filed a request for reconsideration. Please refer to section 7.1.3.4 for details.

11.5.8. Requests for Reconsideration Filed by the Drug Programs

CDA-AMC provides an opportunity for sponsors to comment on requests for reconsideration that are filed by the public drug programs. Sponsors will be notified regarding the request for reconsideration once it has been accepted by CDA-AMC and receive a copy of the request for reconsideration. At that time, the sponsor can provide a written commentary on the request that the has been filed by the drug programs. Commentary should be filed using section 2 of the request for reconsideration template within 5 business days of receiving notification from CDA-AMC (as directed in the correspondence). The completed template will not be posted on the website.

11.5.9. Addressing the Reconsideration Request

11.5.9.1. Request for Major Revisions

The committee briefing materials to address the reconsideration request, include but are not limited to:

- the request for reconsideration
- the feedback from patient groups on the draft recommendation
- the feedback from clinician groups on the draft recommendation
- the draft expert committee recommendation
- the original committee brief for the drug that is the subject of the request for reconsideration
- a summary of input on the request for reconsideration from the following (as applicable): clinical experts, review team, the drug programs (if request is filed by the sponsor), the sponsor (if the request is filed by the drug programs)

- a summary of the reconsideration meeting with the sponsor (if applicable).

The reconsideration brief is delivered to all members of the expert committee members and the drug programs at least 10 business days before the scheduled expert committee meeting.

If the expert committee needs clarification from the review team or the sponsor, or advice from external experts, to address the request for reconsideration, the matter will be sent back to CDA-AMC staff to collect such clarification or advice. Consideration of the drug under review will be moved forward to the next expert committee meeting, pending the collection of the necessary information. No one attending the expert committee meeting may introduce new information.

The expert committee will consider all recommendation categories as described in section 11.5.2 irrespective of the category of recommendation used for the original draft recommendation issued to the drug programs and the sponsor. The expert committee will determine if the original recommendation should be upheld or changed.

Either a final recommendation or a revised draft recommendation will be issued to the sponsor and drug programs 8 to 10 business days following the expert committee meeting.

A revised draft recommendation will be issued in situations where the committee's recommendation has been substantially revised following a request for reconsideration. Specifically, this process will apply in the following circumstances:

- an initial draft recommendation stating that a drug should not be reimbursed was revised to state that the drug should be reimbursed with or without conditions.
- an initial draft recommendation stating that a drug should be reimbursed with or without conditions was revised to state that the drug should not be reimbursed.

A final recommendation will be issued in situations where the draft recommendation has been upheld or has only undergone modifications to the recommended reimbursement criteria, reasons for recommendation, or other changes regarding the description in the recommendation document. When a revised draft recommendation is issued, the options available to the drug programs and the sponsor in the additional feedback period will be the same as those currently described in the section 11.4.2.

The procedure for issuing a final recommendation following a request for reconsideration is described in section 11.6.

11.5.9.2. Request for Minor Revisions

CDA-AMC will convene a panel of expert committee members to review the minor reconsideration request filed by the sponsor and/or drug programs. The panel will typically be composed of the expert committee chair, lead presenter(s), and patient and public members, with additional support from clinical experts, as required. As with full expert committee meetings, the drug programs may observe the deliberations and provide insight into any potential implementation issues with recommendation.

The panel will be provided with briefing materials to address the reconsideration request, including but not limited to:

- the request for reconsideration
- the feedback from patient groups on the draft recommendation
- the feedback from clinician groups on the draft recommendation
- the draft expert committee recommendation
- the original committee brief for the drug that is the subject of the request for reconsideration
- a summary of input on the request for reconsideration from the following (as applicable): clinical experts, review team, the drug programs (if request is filed by the sponsor), the sponsor (if the request is filed by the drug programs)
- a summary of the reconsideration meeting with the sponsor (if applicable).

The expert committee subpanel will focus their deliberations on the issues raised in the request for minor revisions and will not consider all the recommendation categories described in section 11.5.2. The final decision on whether to revise or uphold the recommendation will be made based on consensus and will be documented by CDA-AMC. In the event the subpanel determines that the issues raised in the reconsideration request require deliberation by the full expert committee, the sponsor will be notified and provided with an opportunity to refile the request as a major reconsideration or withdraw the reconsideration and accept the recommendation.

The final recommendation will be issued 8 to 10 business days after the expert committee subpanel has reached a decision on whether to modify to uphold the recommendation. The procedure for issuing a final recommendation following a request for reconsideration is described in section 11.6.

11.6. Final Recommendations

11.6.1. Issuing the Final Recommendation

The final recommendation will be issued in the following circumstances:

- If neither the sponsor nor the drug programs file a request for reconsideration during the feedback period within the specified time, the final recommendation will be issued 8 to 10 business days after the feedback period has ended.
- In the case of a request for reconsideration based on major revisions, the final recommendation will be issued 8 to 10 business days after the expert committee meeting where the draft recommendation has been upheld or has only undergone modifications to the recommended reimbursement criteria, reasons for recommendation, or other changes regarding the description in the recommendation document.

- In the case of a request for reconsideration based on minor revisions, the final recommendation will be issued 8 to 10 business days after the expert committee subpanel has reached a decision on whether to modify or uphold the recommendation.
- In the case of a request for reconsideration that is not accepted, the final recommendation will be typically issued 5 business days after the decision not to accept the request for reconsideration has been communicated to the sponsor.

When a final recommendation is issued, CDA-AMC will send a notice of the final recommendation and a copy of the final recommendation to the sponsor and the drug programs.

11.6.2. Posting the Final Recommendation and Feedback on Draft Recommendation

All final recommendations and feedback on the draft recommendation are posted on the CDA-AMC website. Before these documents are posted, sponsors are responsible for identifying and requesting the redaction of any confidential information. Sponsors must identify any confidential information using the identification of confidential information form. All requests for redaction must be accompanied by a clearly stated rationale. Sponsors must submit the completed form via “5. CDA-AMC Review Reports and Recommendations” folder on the Pharmaceutical Submissions SharePoint site by the date and time specified in the notice of the final recommendation by end of business day (4:00 p.m. Eastern time) 2 business days after the final recommendation was issued.

If the sponsor requests that confidential information be redacted from the final recommendation and the feedback on the draft recommendation, confidential information will be redacted in accordance with the Reimbursement Review Confidentiality Guidelines (typically one business day after receiving the identification of confidential information form from the sponsor). Pursuant to the Reimbursement Review Confidentiality Guidelines, CDA-AMC will indicate that confidential information was used to make the reimbursement recommendation, and that the sponsor requested that this information be kept confidential.

CDA-AMC will distribute responses to the redaction requests for validation by the sponsor. The sponsor will have one business day to validate the redactions. In the case of a disagreement expressed by the sponsor regarding redactions made in the final recommendation or feedback on the draft recommendation, additional time may be required to resolve the disagreement in consultation with the sponsor. This additional time could delay the timeline for posting the final recommendation.

Table 29 summarizes the target timelines for issuing and posting the final recommendation. The feedback on the draft recommendation would be posted at the same time as the final report and supplemental material.

Table 29: Target Timelines for Issuing and Posting Final Recommendations

Key milestones	Description
Final recommendation issued to sponsor and drug programs	No reconsideration: The final recommendation is issued 8 to 10 business days after the end of the feedback period.
	Following reconsideration: The final recommendation is issued 8 to 10 business days after the expert committee meeting where the recommendation was upheld following a request for reconsideration.
Sponsor identifies confidential information	The sponsor has 2 business days to identify any confidential information in the final recommendation using the CDA-AMC template.
Redaction of confidential information	Confidential information will be redacted 1 business day after receipt of the completed template from the sponsor.
Sponsor validates redactions	The sponsor has 1 business day to validate redactions in the recommendation after receipt from CDA-AMC.
Posting on website	The final recommendation will be posted on the website 7 business days after the redactions have been validated by the sponsor.

12. Temporary Suspension and Withdrawal

12.1. Pausing the Clock During Health Canada Review

Sponsors are required to provide notification once a pause-the-clock request has been accepted by Health Canada. At that time sponsors are required to provide the following information:

- The specific issues being addressed by the sponsor while the clock is paused (please note that details are not required and should not be provided to CDA-AMC for any issues related to the quality review by Health Canada [e.g., chemistry, manufacturing, and controls]).

The revised target timelines for the regulatory review process.

- CDA-AMC will review the issues being discussed between the sponsor and Health Canada and determine the following:
- If the issues are not anticipated to have a significant impact on the reimbursement review (e.g., not anticipated to affect the indication or dosing information), CDA-AMC may elect to continue with the review in accordance with the existing timelines.
- If CDA-AMC believes the issues may have an impact on the reimbursement review, the review may be suspended in accordance with section 12 pending clarification of the outstanding information.

In either of the above scenarios, the target expert committee meeting date may be revised to better align with the revised regulatory review timelines.

12.2. Suspension Due to Incomplete Information

If CDA-AMC is unable conduct a thorough review and/or an appraisal due to incomplete information, CDA-AMC, in its sole discretion, may temporarily suspend a review in the following manner:

- CDA-AMC may temporarily suspend a review pending receipt and acceptance of all required information.
- The sponsor will be advised in writing that the review has been suspended. CDA-AMC will indicate what information is required to re-initiate the review process.
- The review report will not be sent to the sponsor for comment and the application will not be placed on the agenda for the expert committee until the review team is satisfied that the sponsor has provided all the required information.
- Once the issue is resolved, depending on the availability of resources, the review will resume at the stage where it was suspended. The sponsor will be advised, in writing, when the review process resumes, along with the anticipated target dates for the remaining steps of the review process.
- A review may be suspended at any stage until the review process has been completed.
- A review that has been suspended is tracked on CDA-AMC's website.

12.3. Suspension Following an NOD or NON

For submissions filed on a pre-NOC basis that receive an NOD or NON from Health Canada, CDA-AMC will allow the review of certain submissions to be suspended while resolution of the NOD or NON is discussed with Health Canada. To be eligible for suspension rather than withdrawal, sponsors must have consented to the information-sharing process between CDA-AMC and Health Canada. CDA-AMC will also consider the following factors when determining if suspension is an option, including but not limited to:

- Health Canada's rationale for the NOD or NON (e.g., clinical versus quality issues)
- the anticipated timelines for addressing the issues raised by Health Canada.

For drugs that undergo temporary suspension because of an NOD or NON, the following information would be required for the suspension to be lifted:

- a summary of the issue and how the sponsor has or is planning to resolve the issue (please note that details are not required and should not be provided to CDA-AMC for any issues related to the quality review by Health Canada [e.g., chemistry, manufacturing, and controls])
- any new clinical data filed with Health Canada to address the issue.
- advance notification of a minimum of 6 weeks from the sponsor when the issue is likely to be resolved and the anticipated date that an NOC or NOC/c may be issued by Health Canada.

Depending on the availability of resources, CDA-AMC will resume the review at the stage where it was suspended. The sponsor will be advised, in writing, when the review process resumes, along with the anticipated target dates for the remaining steps of the review process.

The decision to allow a suspension rather than a mandatory withdrawal will be made solely at the discretion of CDA-AMC on a case-by-case basis. If CDA-AMC determines that a temporary suspension is not appropriate, the submission will have to be withdrawn (in accordance with section 12.5). When deciding if a review can continue, CDA-AMC will consider the following factors:

- **New clinical report required:** The scope of the changes to the indication are sufficiently broad that the existing clinical report is no longer informative and cannot be used for the review (e.g., CDA-AMC would need to appraise and interpret different clinical data given the change to the indication).
- **New economic report required:** CDA-AMC would be required to prepare a new economic report focusing on the revised patient population.
- **New consultation with clinical specialists required:** CDA-AMC would need to reconvene the clinical specialists who are advising on the application to discuss different clinical data and/or potential revisions to the proposed in therapy.
- **New jurisdictional input required:** CDA-AMC would be required to seek updated jurisdictional input to reflect the revised indication (i.e., additional consultation with FWG or PAG).
- **New call for patient and clinician input required:** CDA-AMC would be required to issue a new call for patient and clinician group input (i.e., existing input no longer reflects the target patient population).

12.4. Suspension for Other Reasons

If questions or issues outside of the regular review process arise (for example, but not limited to, legal issues) regarding the drug under review, CDA-AMC, in its sole discretion, may temporarily suspend the review in the following manner:

- CDA-AMC will advise the sponsor in writing that the review has been suspended. CDA-AMC will indicate the anticipated duration of the suspension period. As it is necessary, CDA-AMC has the discretion to extend the temporary suspension.
- CDA-AMC's decision to temporarily suspend a review that was filed on a pre-NOC basis is made independently of Health Canada's review of that drug.
- Once the issue is resolved, depending upon the availability of resources, the review will resume at the stage where it was suspended. The sponsor will be advised by CDA-AMC, in writing, when the review process resumes, along with the anticipated target dates for the remaining steps of the review process.

- The review may be suspended for reasons outside of the regular review process during any stage of the review process.
- A review that has been suspended is tracked on the CDA-AMC website.

12.5. Withdrawal Procedure

An application will be withdrawn from the reimbursement review processes if:

- The sponsor voluntarily requests withdrawal from the CDA-AMC process.
- The sponsor has withdrawn from the Health Canada review process.
- Health Canada has withdrawn market authorization.
- Health Canada has issued a Notice of Deficiency — Withdrawal or Notice of Non-Compliance — Withdrawal.
- Health Canada has issued a Notice of Non-Compliance or Notice of Deficiency, and the sponsor has not or will not consent to the information-sharing process.
- CDA-AMC determines that temporary suspension following the issuance of a Notice of Deficiency or Notice of Non-Compliance is not appropriate.

A sponsor may request voluntary withdrawal from the reimbursement review process at any time up to 4:00 p.m. Eastern time 3 business days before the target expert committee meeting is scheduled. Voluntary withdrawal will not be permitted after this time.

In all cases where marketing authorization has been withdrawn or will not be issued by Health Canada, the sponsor must advise CDA-AMC, in writing, within 1 business day. CDA-AMC appreciates that sponsors may need to manage communications regarding withdrawn files; as a result, when requested, delayed posting of the withdrawn status on the CDA-AMC website can be accommodated. Please ensure that such requests are clearly stated within the correspondence to CDA-AMC.

All requests for withdrawal from the reimbursement review process must be provided in writing and contain the following information:

- name and signature of the sponsor.
- reason for the withdrawal (please note that the reason will not be posted on the CDA-AMC website)
- if market authorization was withdrawn, the date on which market authorization was withdrawn.

CDA-AMC will stop the review immediately upon being notified of a withdrawal or non-issuance of market authorization. CDA-AMC will advise the sponsor and drug programs that the review has been withdrawn. The CDA-AMC website will be updated to state that the application has been withdrawn.

Sponsors that withdraw from the reimbursement review process may be entitled to receive a partial refund of the application fees in accordance with the Fee Schedule for Pharmaceutical Reviews.

CDA-AMC will retain and/or dispose of materials associated with the withdrawn application (as described in Appendix 1).

12.6. Refiling After Withdrawal

The sponsor is required to refile a complete application in accordance with section 6. The refiled application must include a list of the changes made as compared with the initial application that was withdrawn. All updated documents (not limited to new information — e.g., an updated product monograph) must be provided.

In the case of a withdrawn submission for a drug that was previously filed on a pre-NOC basis and that has subsequently received market authorization from Health Canada (NOC or NOC/c), the sponsor is required to file the submission on a post-NOC basis.

CDA-AMC will determine the appropriate approach for conducting the review of an application that has been withdrawn and refiled based on where the previous review was stopped and the amount of new information.

Drug Program Initiated Reviews

13. Non-Sponsored Reimbursement Review Procedures

13.1. Eligibility

This section provides general guidance regarding eligibility for the majority of non-sponsored applications. In some situations, our organization may consult with Federal, Provincial, and Territorial governments and their drug programs to decide on a case-by-case basis.

Public drug programs may request a non-sponsored reimbursement review in situations where a potentially eligible sponsor does not file an application (e.g., submission, resubmission, or reassessment) through our sponsored reimbursement review process. To warrant a non-sponsored review and recommendation from the CDA-AMC, interest from a jurisdiction is required from the applicable CDA-AMC advisory committee (the Formulary Working Group [FWG] or the Provincial Advisory Group [PAG]). For a drug to be eligible for a non-sponsored reimbursement review and recommendation, publicly available evidence of expired or impending loss of exclusivity, as indicated by the Health Canada patent register and/or register of innovative drugs is required.

Before initiating a non-sponsored reimbursement review, we will confirm with the Drug Identification Number (DIN) holder of the branded product that they are declining to file an application with the CDA-AMC (in accordance with section 2.7). However, if the drug under review already has generics or biosimilars approved and marketed, DIN holders will not be contacted.

We will consider reviewing a drug through the non-sponsored reimbursement review process when:

- public drug programs, through the CDA-AMC's advisory committees, request a review and reimbursement recommendation from our Formulary Management Expert Committee (FMEC);
- sponsors of the branded drug have declined to file an application with the CDA-AMC on the basis that competition from generic and/or biosimilar products is imminent;
- the drug is later in its life cycle based on publicly available Health Canada resources (patent register and/or register of innovative drugs); or
- genericized or biosimilar drugs are available, and the reference drug did not have a previous CDA-AMC reimbursement review for the indication of interest and/or new evidence has emerged and the sponsor declines to file a resubmission or reassessment with us.

When sponsors of the branded drug have declined to file an application with the CDA-AMC, we will consider reviewing a drug through the non-sponsored reimbursement review process for clinical indications for which a pharmaceutical manufacturer has not applied for a Health Canada Notice of Compliance (i.e., off-label use) when there is evidence of use of the drug for the condition of interest and experience of use in Canadian clinical practice (e.g., integration of the drug into clinical practice guidelines, consultations with clinical specialists). If requested from public drug programs, drugs will be eligible when at least 1 of the following circumstances apply:

- clinical data are available for the indication of interest, to permit the CDA-AMC and the expert committees to evaluate the effectiveness of the drug;
- approval for use of the drug for the indication of interest has been issued by other regulatory authorities (e.g., US FDA or the European Medicines Agency); or
- there are existing international HTA recommendations in favour of reimbursement.

We will prioritize non-sponsored reimbursement reviews based on advisory committee priority, availability of evidence, and capacity.

13.2. Application Requirements

To initiate a non-sponsored reimbursement review, we must receive an official written request from the chair of the CDA-AMC advisory committee (i.e., FWG or PAG). When a non-sponsored reimbursement review is accepted for review, we will post notice publicly. The posting will contain a description of the drug under review and the indication(s) to be reviewed. The draft research protocol to be conducted by our organization will also be posted publicly.

As the review is initiated by public drug programs, no documentation will be required from an industry sponsor, although additional information provided by industry may be considered. For the non-sponsored reimbursement review process, industry refers to all current and future DIN holders (including manufacturers of generic or biosimilar drugs).

13.3. Engagement with Interested Parties

Engagement with interested parties during the non-sponsored reimbursement review will occur in the same manner as sponsored reimbursement reviews, with some minor amendments as described in the following.

13.3.1. Industry Engagement

Industry will have 35 business days from the notice date issued in the CDA-AMC weekly email update to provide input on the non-sponsored application under review. Industry will also have 10 business days to review the draft recommendation and provide feedback in accordance with section 11.4.2. All input must be submitted using the templates provided by the CDA-AMC and must not contain any confidential information (all information included in the template will be considered disclosable by our organization). As the reimbursement reviews are not pharmaceutical industry sponsored, input from industry manufacturers is not required.

13.3.2. Patient Engagement

Open calls for patient input will be solicited, utilized, and posted in accordance with section 7.2. Patient groups will have 35 business days from the notice date issued in the CDA-AMC weekly email update to

provide input. Patient groups and other interested parties will have 10 business days to review the draft recommendation and provide feedback in accordance with section 11.4.2.

13.3.3. Clinician Engagement

13.3.3.1. Clinician Groups

Groups or associations of health care professionals will have 35 business days from the notice date issued in the CDA-AMC weekly email update for preparing and submitting their input. Clinician group input will be solicited, utilized, and posted in accordance with section 7.3.1. Groups or associations of health care professionals and other partners will have 10 business days to review the draft recommendation and provide feedback in accordance with section 11.4.2.

13.3.3.2. Clinical Experts on the Review Team

CDA-AMC review teams will include at least 1 clinical specialist with expertise in the diagnosis and management of the condition for which the drug is indicated, and the potential place in therapy for the drug. The expert(s) will be involved in all phases of the review process in accordance with section 7.3.2.

We may increase the number of clinical experts depending on the complexity of the drug under review. We may also establish a panel of clinical experts to provide insight into the drug's potential place in therapy.

13.3.4. Drug Program Engagement

When a non-sponsored reimbursement review is initiated, public drug programs will provide input on issues that may impact their ability to implement a recommendation. The summary of implementation issues will be presented to FMEC by a lead jurisdiction (or designate). The draft recommendation will be discussed with the applicable advisory group (FWG or PAG) to collate and finalize their feedback.

Table 30: Key Milestones for Interested Parties Engagement

Milestones	Industry, patient group, clinician group	Drug programs	Clinical expert(s)
Request non-sponsored reimbursement review	NA	Public drug programs, with support of applicable CDA-AMC advisory committee (FWG or PAG).	NA
Review phase	Interested parties will have 35 business days from the notice date issued in the CDA-AMC weekly email update to provide input.	We will provide a standardized template for completion by a lead jurisdiction; the initial draft will be discussed and finalized at a scheduled PAG or FWG meeting.	Provide guidance on the development of the review protocol. Assist in the critical appraisal of clinical evidence and guidance on the potential place in therapy. Advise on the assumptions used in the economic review. Advise on implementation issues raised by jurisdictions.
Feedback on recommendations	There will be 10 business days to review and comment on the draft recommendations during the interested parties feedback period.	Provide feedback on draft reimbursement recommendations. Eligible to file a request for reconsideration.	Provide feedback on draft reimbursement recommendations. If necessary, provide input on requests for reconsideration.
Implementation phase	NA	Drug programs may request an additional CDA-AMC product to facilitate the implementation of the recommendation.	As part of an implementation advice panel, experts may advise on outstanding implementation issues and further develop and refine reimbursement conditions. Advise on treatment sequencing within a particular indication for oncology drugs.

FWG = Formulary Working Group; NA = not applicable; PAG = Provincial Advisory Group.

13.4. Review Procedure

13.4.1. Clinical Review

At the initiation of the review, our organization develops a protocol to ensure that the review will reflect the most relevant clinical information. The protocol specifies the following aspects of the review:

- the populations, intervention, comparators, outcomes, and study designs that will be used to conduct a systematic literature review
- any supplemental information that will be included in the review to provide additional context (e.g., description, evidence of validity, and clinical importance of the outcome measures), if known at the time the research protocol is finalized. Supplemental materials may be included after the protocol is final if it is deemed appropriate by the clinical review team.
- any relevant evidence that will be included but not be captured in the systematic literature review (e.g., indirect comparisons, long-term extension studies, and studies of other designs that address important gaps in the clinical trial evidence).

When drafting the review protocol, we consider a variety of information, such as clinical practice guidelines, the availability of comparator drugs, clinical trial protocols, and input from interested parties (i.e., information from patient groups, clinical experts, drug programs, and expert committee members). Any clinical end points that were identified by patient groups as being particularly relevant for those living with the condition will be added to the protocol document.

CDA-AMC conducts 1 or more independent systematic literature searches according to the protocol. The search strategy used and the relevant literature that is identified are included in the clinical review. We summarize and critically appraise the relevant studies in the clinical report. Strengths and limitations with respect to both internal validity (i.e., how well the study was designed, conducted, and reported) and external validity (i.e., how well the results of the study could be applied to the target population in Canada) are documented.

Patient and clinician group input are included in the clinical report. When discussing the available evidence, our organization reflects on the input from patient and clinician groups, particularly any areas where there is an unmet therapeutic need for those living with the condition; known advantages and disadvantages of the treatments that are currently available; and any expectations regarding new therapies (including the drug under review).

To accommodate the absence of an industry sponsor:

- DIN holders will not have the opportunity to review and comment on the draft clinical review report before the expert review committee.
- DIN holders will not have the opportunity to review and request the redaction of any information in the clinical report before it is posted on the CDA-AMC website.

13.4.2. Economic Review

In the absence of an application filed by an industry sponsor, our organization does not have access to an economic model for the drug under review. As a result, the economic review will include a comparison between the costs of the drug under review and those of appropriate comparators.

In the absence of an industry sponsor, DIN holders will not have the opportunity to review and comment on the draft economic report before the expert review committee. If additional information from outside the public domain is provided by industry, we will not provide an opportunity to review and request redactions before posting on the CDA-AMC website.

13.5. Deliberative Framework

The expert committee and subcommittee deliberations are guided by the deliberative framework in the Expert Committee Deliberation at Canada's Drug Agency document. The deliberative framework consists of 5 domains of value that are relevant for the expert committee to consider in their deliberations: clinical value, unmet clinical need, distinct social and ethical considerations, economic considerations, and impacts on health systems.

13.6. Recommendation Procedure

The output from the non-sponsored reimbursement review process will be a reimbursement recommendation from FMEC. Our organization’s recommendations from the non-sponsored reimbursement review process will be issued based on the active substance to accommodate scenarios where there are or will be multiple DIN holders.

13.6.1. Recommendation Framework

FMEC will apply the recommendation framework in accordance with 11.3.2.

13.6.2. Draft Recommendations

In accordance with the process described in section 11.4.2, draft recommendations will be posted for feedback for 10 business days. The drug programs, patient groups, clinician group(s), and DIN holders for the drug under review may provide feedback on the draft recommendation using the applicable CDA-AMC template.

13.6.3. Reconsideration

The participating drug programs may file a request for reconsideration of the draft recommendation. In the absence of an industry sponsor, DIN holders will not have the opportunity to request reconsideration of the draft recommendation; however, their feedback on the draft recommendation may be considered if a reconsideration has been requested by the drug programs.

13.7. Transparency and Engagement with Interested Parties

In accordance with our existing reimbursement processes, the following information will be posted on the CDA-AMC website for non-sponsored reimbursement reviews:

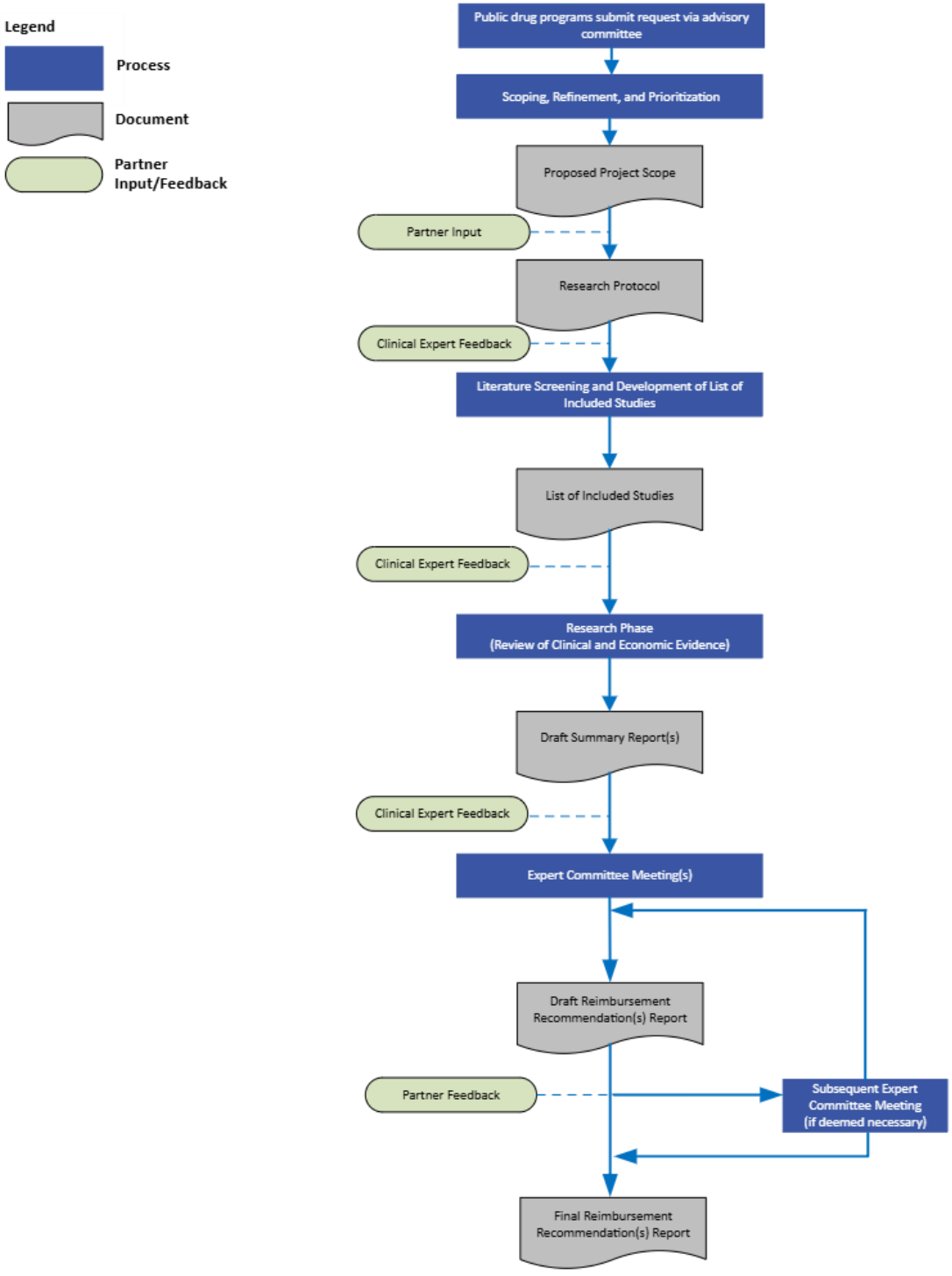
- calls for patient and clinician group input
- key dates of the non-sponsored reimbursement reviews
- CDA-AMC reports and reimbursement recommendations
- Interested party feedback on the draft recommendation.

As previously stated, all information submitted by interested parties will be considered disclosable by our organization. DIN holders will not have the opportunity to review and request redactions of CDA-AMC reports or recommendations before they are posted on the CDA-AMC website.

In the non-sponsored review process, input or feedback from interested parties is solicited at the following stages:

- proposed project scope
- draft reimbursement recommendations report

Figure 4: Overview of Nonsponsored Reimbursement Review Process



14. Requests for Advice

14.1. Eligibility

The Request for Advice (RFA) process will typically be applied when public drug programs or the pCPA raise issues or require clarification on conditions and/or criteria to an existing reimbursement recommendation in light of contextual or practice changes that impact the ability of drug programs to implement an existing reimbursement recommendation.

Drug manufacturers and tumour groups are not permitted to initiate the RFA process.

We will consider an RFA when public drug programs or the pCPA, through 1 of the CDA-AMC pharmaceutical advisory committees, request a review of a condition(s) or criteria, or require clarification to a previously issued reimbursement recommendation.

An RFA can:

- provide clarity and updates to previous reimbursement conditions and criteria (e.g. clinical practice has changed since the previous reimbursement recommendation and the reimbursement criteria is no longer implementable)
- address an implementation question(s) that was not considered at the time of the original review (e.g., subgroups that were not explicitly identified in clinical trials and therefore not highlighted within reimbursement recommendations).

A RFA will not:

- change the overall recommendation status for a drug (i.e., from a do not reimburse recommendation to a recommendation in favour of reimbursement) by reconsidering previously evaluated evidence by 1 of CDA-AMC expert committees.

If new studies support revisions to the reimbursement criteria for the drug and indication under review, then a reassessment, resubmission, or a nonsponsored reimbursement review may be required.

14.2. Application Requirements

To initiate the RFA process, we must receive an official written request from the applicable advisory committee chair (the FWG or PAG). The formal request must outline the relevant issue(s) that are to be addressed in the review and question(s) to be answered, if possible, by the expert committee.

As the review is initiated by public drug programs, no documentation will be required from an industry sponsor, although additional information provided from industry may be considered. Any information provided by manufacturers as part of the RFA process, including unpublished data, will not be subject to redactions.

14.3. Engagement With Interested Parties

14.3.1. Industry, Patient, and Clinician Engagement

When an RFA is accepted for review, the project scope will be posted on the CDA-AMC website. The project scope will include:

- the drug and indication
- the reimbursement recommendation for which the request pertains to
- the question(s) being asked by the public drug programs or pCPA.

Interested parties will be notified through the Weekly Summary email of active RFAs. Opportunities for input from interested parties can be found on the CDA-AMC website under Open Calls for Input and Feedback. Health system partners, including manufacturers, will have 10 business days to provide written input on the project scope. This input must be submitted using the template provided and must not contain any confidential information (all information included in the template will be considered disclosable). No requests for extensions are granted. Refer to sections 7.2 and 7.3 for additional details on patient and clinician engagement, respectively.

Input or feedback from interested parties will be solicited through an open call on our website at the following stages of the review: project scope and draft advice.

14.3.2. Industry Engagement

The manufacturer(s) of the drug(s) (i.e., DIN holder) are apprised of the RFA and the target dates for providing input. While notice of the proposed RFA is posted on the CDA-AMC website, we may notify affected manufacturers directly.

14.3.3. Experts on the Review Team

If deemed necessary based on the question(s) outlined in the request, CDA-AMC may include a clinical expert(s) with expertise in the diagnosis and management of the condition for which the drug is indicated to support the review. Clinician expert(s) may be invited to attend the expert committee meeting for which the review will be discussed, if required.

14.4. Research Phase

Given an RFA may be conducted for varying reasons to address changes in the disease paradigm and other contextual factors (e.g., regulatory actions, changes in clinical practice such as diagnostics or testing), CDA-AMC will determine the appropriate approach for completing the RFA. The source and type of relevant evidence may vary.

We will establish a protocol for the review and may conduct 1 or more literature searches to identify relevant information and confirm no new clinical trials have been conducted to address the policy question that may warrant a review through our nonsponsored reimbursement review, resubmission, or reassessment processes. The studies and materials identified through the literature search, as well as any information or data provided by the manufacturer(s), will be included as part of the review. If additional information from outside the public domain is provided by industry, and is used by CDA-AMC, we will not provide an opportunity to review and request redactions before posting on our website.

- Evidence may include, but is not limited to:
- evidence-based clinical practice guidelines, and references within these
- expert opinion (e.g., where there is no new generated evidence in the form of clinical trials)
- published HTA assessments within Canada or internationally

14.5. Draft Updated Reimbursement Recommendations

The output from an RFA will be an updated reimbursement recommendation report issued by our expert committee. RFAs will be reviewed and issued an updated reimbursement recommendation, where applicable, by FMEC. We may consult with members from the initial committee who issued the recommendation (i.e., CDEC, pERC, or FMEC) for input and consideration as part of the RFA process, if required.

In accordance with the process described in section 11.4, a draft updated recommendation will be posted for feedback from interested parties for 10 business days. Patient groups, clinician groups, and industry partners may provide feedback on the draft updated recommendation using the applicable template.

Given that the updated reimbursement recommendation may impact existing conditions and criteria set out in a previous reimbursement recommendation, information within the RFA report will supersede the existing reimbursement recommendation.

Multiple Drug Reviews

15. Streamlined Reviews

15.1. About Streamlined Reviews

A streamlined review is a form of CDA-AMC Therapeutic Review that leverages published clinical information to provide decision-makers with timely evidence to support drug policy decisions and formulary management. The focus of each review will be on a therapeutic disease area (e.g., management of hypertension), category of drugs (e.g., antihyperglycemia drugs), or a class of drugs (e.g., sodium-glucose cotransporter-2 inhibitors). The purpose of the streamlined review is not to replace the CDA-AMC therapeutic review, but to leverage existing published evidence when de novo meta-analyses or economic analyses are not required to support more timely decision making.

The primary outputs from a streamlined review will be a summary report (which includes a clinical and economic assessment) and a reimbursement recommendation report. The recommendation report will include a reimbursement recommendation from FMEC.

15.2. Target Audience and Application for Decision-Making

Streamlined reviews are undertaken to inform federal, provincial, and territorial government drug programs, including those from provincial cancer agencies, administrators and health policy-makers working at regional health authorities, and staff at hospitals in Canada who make decisions about the optimal use of, access to, or reimbursement of pharmaceuticals. Streamlined reviews are not meant to replace professional medical advice. Readers are also cautioned that a lack of good-quality evidence does not necessarily mean a lack of effectiveness, particularly in the case of new health technologies for which little evidence is available but may prove to be effective in the future.

15.3. Streamlined Review Process

15.3.1. Topic Identification and Refinement Phase

15.3.1.1. Topic Identification

Topic identification includes both reactive projects (i.e., those for which a specific request was received from a CDA-AMC customer) and proactive projects (i.e., projects identified by our organization in anticipation of evolution within a therapeutic space or drug class that may have a significant impact on the Canadian publicly funded health system). The following criteria will be assessed during the scoping phase to determine feasibility for a Streamlined Review:

- Robust published evidence of clinical effectiveness, which could include existing head-to-head data or high-quality existing systematic review(s) and meta-analyses of relevant clinical outcomes (e.g., from another HTA agency). Published evidence that is recent and includes the necessary comparators to inform the policy question will be considered.

- Utilization analyses demonstrate that there may be an opportunity to improve optimal use.
- One or more of the drugs are later in their lifecycle, based on publicly available Health Canada resources (patent register and/or register of innovative drugs).
- In alignment with the CDA-AMC Therapeutic Review procedures, topics are also selected and prioritized based on the result of a CDA-AMC drug reimbursement recommendation.

15.3.1.2. Topic Scoping and Refinement

Our organization refines topics through jurisdictional working groups comprised of representatives from public drug programs and clinical experts. We develop a project proposal that contains an initial scoping literature search (including existing recommendations from the CDA-AMC single drug review processes for drugs to be included for review, if applicable), discussions with the jurisdictional representatives, and consideration of factors such as relevance, timeliness, and potential impact (Table 31 in the Therapeutic Review section of this document). In circumstances when recent CDA-AMC Health Technology Reviews have been completed and demonstrate opportunities for formulary management (e.g., Integrated Technology Review), these reports may be leveraged as the project proposal. Public drug programs review the proposals and establish priority of the streamlined review topics.

We will include equity, diversity, and inclusion considerations in the evidence and input collected from interest partners. The largest differentiation between therapeutic reviews and streamlined reviews relates to the review of clinical and economic evidence (described below).

If a topic is supported by jurisdictions, a Proposed Project Scope document is posted on the CDA-AMC website for input from interested parties (typically for a period of 10 business days) (i.e., patients, health care providers, and pharmaceutical companies). The Proposed Project Scope will outline the policy questions, research questions, selection criteria, included studies (to be summarized and appraised in the review) if available, methodology, and search strategy. The literature search will be conducted in accordance with the Therapeutic Review procedures (section 16.3). Input on the included publications is also obtained from advisory committee discussants and clinical experts. Input includes, but is not limited to, assisting in the development of research questions, identifying relevant outcomes, identifying subgroups of potential interest, and identifying any methodological weaknesses of the included publications.

While notice of the proposed review is posted on the CDA-AMC website, affected manufacturers and partners, including patient groups, may be notified directly by our organization. Our partners may comment on the proposed project scope or share concerns with the list of included studies. All input and feedback are reviewed by our organization and is used to finalize the scope of the review. Based on feedback from interested parties, we refine the proposed project scope document and obtain final advice from the public drug programs on whether to proceed.

15.3.2. Research Protocol

Once the project scope is finalized, we create the project research protocol. The research protocol addresses the scope of the project and the methodologies to be used, incorporating any necessary changes based on input received. The final research protocol is posted on the CDA-AMC website for information purposes only.

15.3.3. List of Included Studies

The list of included studies incorporated in the final Summary Report may be revised if additional information is provided following input and feedback from interested parties on the Proposed Project Scope and will be based on the final research protocol. The primary evidence evaluated for possible inclusion in a streamlined review is retrieved from publicly available scientific research sources, such as peer-reviewed scientific journals and grey literature sources. Sources of evidence may include:

- HTAs
- systematic reviews
- network meta-analyses
- published findings of clinical studies
- clinical guidelines
- comments, newspaper articles, editorials, and letters are excluded.

Interested partners are given the option of identifying and providing unpublished data for consideration in the streamlined reviews on the condition that, if used, it will be included in publicly available reports and documents related to the review and will not have the opportunity to request redactions.

15.3.4. Research Phase

15.3.4.1. Review of Clinical Evidence

A streamlined review leverages published meta-analyses or other published evidence rather than de novo CDA-AMC analyses. Included publications are critically appraised by our organization based on the best available methods, and a summary of the collective findings presented in the Summary Report. Clinical guidelines may also be discussed in the summary report. The draft Clinical Summary Report is internally reviewed.

15.3.4.2. Review of Economic Evidence

Streamlined reviews will not include de novo cost-utility analyses. When applicable, the economic review may leverage existing published models or economic models from previous CDA-AMC Therapeutic/Technology Reviews. If appropriate, the review may include a cost comparison and a pan-Canadian budget impact analysis.

15.3.4.3. Drafting the Summary Report

The Summary Report will include a combined clinical and pharmacoeconomic report. In addition to the clinical and economic evidence described above, the summary report may also include or reference other CDA-AMC reviews, such as, but not limited to, a CDA-AMC Integrated Technology Review, utilization report, Horizon Scan, and/or Environmental Scan that has been conducted in the therapeutic area, if available.

The draft Summary Report is posted for feedback on the CDA-AMC website. The time allotted for comments is 10 business days. The feedback is then reviewed, and the report is revised based on the feedback (as required). The final Summary Report is shared with the expert committee as part of their meeting package to help inform deliberations and decisions.

15.4. Recommendations Phase

15.4.1. Draft Streamlined Review Recommendations

The expert committee hears presentations of the input from patients and caregivers, clinical and economic evidence (Summary Report), input from clinical experts, and implementation considerations at the jurisdictional level. All committee members can ask questions or make comments. Input and feedback received from interested parties is also shared with the expert committee Clinical experts involved in the Streamlined Review are available to answer questions and to comment on the evidence presented. There are 2 primary objectives of this meeting:

- to develop draft recommendations or advice to address the policy and research questions that were raised by the public drug programs at the outset of the streamlined review process
- to propose revisions to existing recommendations from our organization's reimbursement review process (if applicable, based on the outcome of the streamlined review)

A recommendations report will summarize the recommendations and/or advice, the reasons for the recommendations, patient perspectives, the clinical and economic evidence that was discussed, and the research gaps that were identified by the committee. The draft Streamlined Review reimbursement recommendations report and a document summarizing the committee's proposed revisions to any existing CDA-AMC reimbursement recommendations (if applicable) are posted on the CDA-AMC website for feedback from interested parties for a period of 10 business days. If available, the final Summary Report is also posted for informational purposes.

15.4.2. Final Streamlined Review Recommendations

Our organization and the chair of FMEC meet to discuss the feedback from interested parties. If deemed necessary by the committee chair, further discussion(s) with the expert committee will happen or be held at the next scheduled expert committee meeting. The expert committee then finalizes the

recommendations and/or advice statements. A summary of the feedback considered is included within the final recommendations report.

15.4.3. Revised CDA-AMC Reimbursement Recommendations

One of the outputs from our Streamlined Review may be revised recommendations for drugs that have previously been reviewed through the CDA-AMC reimbursement review processes.

15.4.3.1. Identification of Existing CDA-AMC Reimbursement Recommendations

Existing CDA-AMC reimbursement recommendations that could be revised because of the Streamlined Review will be identified and communicated to our partners during the scoping phase of the review process.

15.4.3.2. Expert Committee Recommendation Process

As part of the deliberative process for a Streamlined Review, FMEC will consider whether or not the results of the review suggest that any existing recommendations that were issued through the reimbursement review process should be revised.

15.4.3.3. Interested Parties Feedback on Revised Recommendations

Proposed revisions to existing reimbursement review recommendations will be posted for feedback from interested parties at the time the draft Streamlined Review recommendations are posted. The following information will be included:

- the drug (generic and brand name where appliable) and CDA-AMC project number of the original reimbursement recommendation
- the date of the reimbursement recommendation
- the original recommendation that may be revised because of the Streamlined Review
- the updated or revised reimbursement conditions being proposed by FMEC (if applicable).

Interested parties will have the opportunity to provide feedback on the proposed revisions to the draft recommendations. There will be no opportunities to request reconsideration of revised reimbursement recommendations through the Streamlined Review procedure. Only public drug programs, through the jurisdictional advisory committees, may request a reconsideration.

15.4.3.4. Consideration of Feedback From Interested Parties

Similar to feedback on the draft Streamlined Review recommendations report, our staff will collate feedback from interested parties on any revisions to existing reimbursement review recommendations. The feedback from interested parties will be presented to the Chair of the expert committee for consideration of revisions based on feedback from interested parties, and if deemed necessary,

discussed by the committee at the next scheduled expert committee meeting for any further revisions based on feedback received.

The committee will consider the feedback, the evidence from the streamlined review, and the final streamlined review recommendations and determine if any existing reimbursement review recommendations should be revised.

Depending on feedback, this could result in revisions that were not initially identified at the time of feedback. We will only issue a second call for feedback from interested parties for revised reimbursement recommendations when the committee's recommendation has been substantially revised following the initial round of feedback. Specifically, this process will apply in the following circumstances:

- the recommendation category has been changed (e.g., from a recommendation that a drug should be reimbursed with or without conditions to a recommendation that the drug should not be reimbursed)
- the reimbursement conditions have been revised to reflect a different place in therapy relative to alternative therapies (e.g., a change to the recommended sequence of therapies)
- the patient population identified in the reimbursement conditions has been substantially altered relative to the initially proposed recommendation (e.g., the population has been narrowed or expanded); in these cases, the expert committee will determine if an additional call for partner feedback is warranted as part of the deliberations.

15.4.3.5. Finalizing Revised Reimbursement Recommendations

When the committee has determined that a previous reimbursement recommendation should be revised because of a streamlined review, we will issue a new final recommendation. The revised recommendation will be an abbreviated document containing the following key information:

- rationale for updates to the reimbursement recommendation(s)
- the recommendation(s), including any conditions (if applicable)
- a statement indicating that the revised recommendation has been issued as a result of a CDA-AMC Streamlined Review
- a disclaimer indicating that the revised recommendation supersedes the previous reimbursement review recommendation(s) for the drug and indication of interest
- a table outlining the drug(s) and the updates or revisions to the reimbursement recommendation(s) by FMEC.

15.4.3.6. Posting Revised Reimbursement Recommendations

The revised final recommendation will contain no confidential information; therefore, manufacturers will not be asked to complete a redaction request form. Any unique information provided to CDA-AMC by

impacted manufacturers, including unpublished information, is subject to being included in CDA-AMC Streamlined Review Summary Report(s) and/or recommendation report(s) with no opportunity for redactions.

15.5. Target Timelines

Please refer to Table 34 for target timelines. Prioritization and timelines will be discussed with public drug programs.

15.6. Transparency and Engagement With Interested Parties

To support and encourage patient groups to participate, groups are invited to a teleconference with CDA-AMC staff early in the process. During the teleconference, the project is described, expectations are identified, and possibilities for patient group involvement in the project are discussed.

We notify interested parties that a Streamlined Review has been initiated and outlines target dates for providing feedback by posting a notice to the Calls for Feedback webpage and issuing an email to subscribers of the CDA-AMC Weekly Summary. Instructions on providing feedback are included with every notification. In the streamlined review process, our organization provides 10 business days for interested parties to provide feedback at the following stages:

- Proposed Project Scope
- draft Summary Report
- draft reimbursement recommendations report
- proposed revisions to existing recommendations from CDA-AMC's single drug review programs (if applicable).

Streamlined Review reports are posted on the CDA-AMC website for anyone to access and review, although in exceptional circumstances, embargo periods may be considered.

16. Therapeutic Review

16.1. About Therapeutic Reviews

A Therapeutic Review is an evidence-based review of publicly available sources regarding a therapeutic category of drugs (e.g., antihypertensive drugs) or a class of drugs (e.g., angiotensin-converting enzyme inhibitors) in order to support drug reimbursement decisions and drug policy decisions, and to encourage the optimization of drug therapy. This requires balancing maximized benefits with minimized risks to people's health based on best-quality evidence, taking into account the options, costs, available resources, patient preferences, and societal context.

Publicly funded drug programs evaluate and consider the addition of new drugs to their formularies. They do this based on favourable efficacy, safety, and cost-effectiveness analyses as reviewed by our pharmaceutical review programs. Therapeutic Reviews may be useful in any scenario where there is uncertainty regarding the comparative clinical effectiveness and cost-effectiveness of drugs in a particular therapeutic category or drug class.

The primary outputs from a Therapeutic Review will typically include the Therapeutic Review Summary Report(s) and Therapeutic Review recommendations report. In addition, the Therapeutic Review process may involve an update to the recommendations that were issued through our drug Reimbursement Review processes by 1 of our expert committees (i.e., pERC, CDEC, or FMEC).

Drug-related recommendations and/or advice from our drug Reimbursement Review processes are provided by appointed expert committees to our organization. The expert committee specifically tasked with reviewing and issuing reimbursement recommendations for Therapeutic Reviews is FMEC.

FMEC is composed of individuals with expertise in drug therapy, drug evaluation, and drug utilization, as well as public and patient members who bring an individual perspective. The current terms of reference and membership are listed on the CDA-AMC website.

16.2. Target Audience and Application for Decision-Making

Therapeutic Review Reports are produced for federal, provincial, and territorial government drug programs, including provincial cancer agencies, administrators, and health policy-makers working at regional health authorities and hospitals in Canada who make decisions about the optimal use of, access to, or reimbursement of pharmaceuticals. Therapeutic Review projects are not meant to replace professional medical advice. Readers are also cautioned that a lack of good-quality evidence does not necessarily mean a lack of effectiveness, particularly in the case of new health technologies for which little evidence is available but may prove to be effective in the future.

16.3. Therapeutic Review Process

16.3.1. Topic Identification and Refinement Phase

16.3.1.1. Topic Identification

Topic identification includes both reactive projects (i.e., those for which a specific request was received from a CDA-AMC customer) and proactive projects (i.e., projects identified by our organization in anticipation of evolution within a therapeutic space or drug class that may have a significant impact on the Canadian publicly funded health system). Factors related to policy issues used to identify potential Therapeutic Review topics include, but are not limited to the following:

- when there is a request to assess the optimal sequence of drugs in a therapeutic area with increasing treatment options, including those that are at or beyond exclusivity

- when a CDA-AMC drug reimbursement recommendation triggers a review of coverage of existing drugs used within the treatment paradigm (i.e., reimbursement policies)
- if a CDA-AMC drug reimbursement recommendation suggests that a Therapeutic Review should be conducted to evaluate the comparative clinical effectiveness and cost-effectiveness of drugs in a particular therapeutic area.

16.3.1.2. Topic Scoping and Refinement

The aim of the Therapeutic Review topic submission and selection processes is to ensure that appropriate topics are identified and selected so that outputs are timely and relevant in addressing priority issues for public drug programs. We refine topics considering factors outlined in Table 31 and through discussions with jurisdictional advisory committees (i.e., the Pharmaceutical Advisory Committee [PAC], FWG, and PAG) on a regular basis. The initiation of a Therapeutic Review will require a formal request signed by the Chair of the appropriate jurisdictional advisory committee.

Table 31: Key Factors Considered in Scoping Potential Therapeutic Review Projects

Factor	Questions for Consideration
Relevance	• What are the policy and/or decision problems under consideration? • What are the reimbursement policies for the drug class targeted for assessment? • How are the drugs of interest currently being used in Canadian practice? • Is there evidence of suboptimal health policy or variation in clinical practice? • Are there significant changes anticipated in the therapeutic area (e.g., robust pipeline of new treatments, drugs at or beyond exclusivity)?
Timeliness	• When are the reports and recommendations required by the jurisdictions? • Are resources available to undertake the proposed Therapeutic Review? • Who are the knowledge partners that may assist with the development and dissemination of the report and recommendations?
Impact	• How could recommendations change clinical practice? • Who is the target population? • What is the Canadian prevalence of the condition(s)? • How could people living in Canada be affected by reimbursement, policy, or behavioural changes that may result from the Therapeutic Review? • What are the health care costs (e.g., direct, indirect, governmental, or societal costs) associated with the drugs of interest? • How could the recommendations from the Therapeutic Review impact health care costs (e.g., change in purchasing decisions, change in drug formulary policy)?

Factor	Questions for Consideration
	• Is there similar work that has been recently published or undertaken by another organization (e.g., other HTA organizations)? If so, are there opportunities for partnerships in research activities and/or the dissemination of the information? • Who are the target audiences for the Therapeutic Review (e.g., patients, policy-makers, clinicians, and/or health care practitioners)? • What is the possibility of changing policy and/or clinical practice?

HTA = health technology assessment.

Following detailed scoping, refinement, and request from a jurisdictional advisory committee, we create a Proposed Project Scope document. The scope is determined by the needs of our jurisdictional customers and includes assisting in the development of policy questions, research questions, and elements that will inform the literature search once the research protocol is finalized. In exceptional circumstances, the project scope may include drugs with evidence-based expanded use (i.e., for a clinical indication for which a pharmaceutical manufacturer has not applied to Health Canada and that is not included in an approved Health Canada product monograph, sometimes referred to as off-label use). Key considerations used when determining whether to include a comparator that does not have regulatory approval from Health Canada for that indication are:

- evidence of use of the drug for the condition of interest in Canadian clinical practice (e.g., integration of the drug into clinical practice guidelines, consultations with clinical specialists)
- availability of data evaluating the efficacy and safety of the drug in an indication for which the manufacturer has not applied or received approval from Health Canada
- evidence of HTA organizations and/or payers having made recommendations or decisions to fund the drug, despite lack of regulatory approval
- approval for use of the drug for the indication of interest has been issued by other regulatory authorities (e.g., FDA or the European Medicines Agency).

The Proposed Project Scope document is posted on the CDA-AMC website for interested parties input (typically for a period of 10 business days). Any interested parties may comment on the Proposed Project Scope. Our organization especially welcomes input on the population, comparators, and outcomes described in the scope, as this is used to inform the research protocol development. All input is reviewed by the CDA-AMC and is used to finalize the scope and research protocol of the Therapeutic Review project. Based on partner input, our organization refines the project scope. In the case of any substantive changes, we obtain final advice from the public drug programs on how to proceed.

Interested parties are notified of the proposed Therapeutic Review and the target dates for providing input. While notice of the proposed Therapeutic Review is posted on the CDA-AMC website, affected manufacturers and partners, including patient groups, may be notified directly by our organization. To support and encourage patient groups to participate, groups may be invited to a teleconference with

CDA-AMC staff in the process. During the teleconference, the project is described, expectations are identified, and possibilities for involvement in the project are discussed.

16.3.2. Research Protocol

Once the project scope is finalized, we create the project research protocol. The research protocol addresses the scope of the project and the methodologies to be used. Input on the draft research protocol is obtained from representatives of the jurisdictional advisory committee and clinical experts. Input includes, but is not limited to, further identifying relevant outcomes and identifying subgroups of potential interest. Once finalized, the research protocol is posted on the CDA-AMC website for information purposes only and may be registered in the PROSPERO international database.

16.3.3. List of Included Studies

Once the results of the clinical literature search have been received, the 2 authors independently screen retrieved titles and abstracts and come to a consensus on what literature to order. Both authors independently review the full-text articles selected, as well as any unique information received from partners. Following this, they come to a consensus on which studies meet the inclusion criteria for the project (as documented in the research protocol). If there is disagreement on the findings, a third clinical researcher is engaged in the analysis. Unique studies identified are added to the project's list of included studies for review.

The list of studies that have been selected as relevant for the Clinical Summary Report, based on the final research protocol, are posted for feedback from interested parties (typically for a period of 10 business days). The list of included studies may be revised depending on the feedback received. The primary evidence evaluated for possible inclusion in a Therapeutic Review is from the public domain. Sources of evidence are described as follows:

- Published literature is identified by searching major biomedical bibliographic databases using an internally peer-reviewed search strategy. Biweekly search updates are run for the duration of the review.
- Grey literature (literature that is not commercially published) is identified by searching relevant sections of the CDA-AMC Grey Matters Checklist, and by consulting internet search engines, web-based materials,
- CDA-AMC web-based resources, and additional web-based materials.
- Clinical experts are engaged and given the opportunity to suggest evidence to be reviewed.
- CDA-AMC will try to contact the manufacturers affected by the review to expand on the existing evidence, unless the drug is already generic or biosimilars have been approved. We inform the recipient in writing about an upcoming Therapeutic Review.

Interested partners are given the option of identifying and providing unpublished data for consideration in the Therapeutic Review on the condition that, if used, the data will be included in publicly available reports and documents related to the Therapeutic Review and will not have the opportunity to request redactions.

16.3.4. Research Phase

Our Therapeutic Review processes reflect nationally and internationally recognized standards and methodologies. New methodologies for assessing drugs are continuously monitored and evaluated, and those that are found to enhance current CDA-AMC processes are incorporated. Therapeutic Reviews are based on the best available evidence for addressing the relevant policy question(s).

16.3.4.1. Review of Clinical Evidence

If sufficient studies are found that meet inclusion criteria with similar populations and outcomes, data are extracted from the included studies to conduct a meta-analysis. The meta-analysis is a statistical summary of the selected studies that tests the pooled data for statistical significance. Both authors critically appraise, analyze, and interpret the clinical data to generate a reproducible, transparent, and rigorous review of the available clinical evidence. The draft Clinical Summary Report is internally reviewed.

16.3.4.2. Review of Economic Evidence

Once the results of the focused economic literature search and unique information from partners (if sent) have been received, we determine whether a new economic model is required to provide information on cost-effectiveness. We then assess the feasibility of undertaking a full economic analysis. Where a model is developed, it will adhere to the *Guidelines for the Economic Evaluation of Health Technologies: Canada* and be based on input from the clinical experts and project team. Data inputs for the model are sought from the published literature or based on available data. If a full economic analysis is not feasible, we will explore other options to assess the economic or financial implications.

16.3.4.3. Drafting the Summary Reports

The review team prepares a draft Clinical and Economic Summary Report. The draft Therapeutic Review Summary Report(s) are posted for feedback and interested partners are invited to provide feedback. The draft reports are posted for feedback on the CDA-AMC website. The time allotted for feedback is 10 business days. Partner feedback is subsequently reviewed, and the report is revised based on the feedback (as required). The final Summary Report(s) are shared with the expert committee as part of their meeting package to help inform deliberations and decisions.

16.3.5. Recommendations Phase

16.3.5.1. Draft Therapeutic Review Recommendations

The expert committee deliberates based on presentations of the input from patients and caregivers, clinical and economic evidence (Summary Report[s]), input from clinical experts, and implementation considerations at the jurisdictional level. Clinical experts involved in the Therapeutic Review are available to answer questions and comment on the evidence presented. There are 2 primary objectives of committee deliberations:

- to develop draft recommendations or advice to address the policy questions that were raised by the public drug programs at the outset of the Therapeutic Review process
- to propose updates and revisions to existing CDA-AMC drug reimbursement recommendations (if applicable, based on the outcome of the Therapeutic Review).

The Therapeutic Review recommendations report summarizes the recommendations and/or advice, reasons for recommendations, values and preferences of the committee members, patient preferences, clinical and economic evidence that was discussed, and research gaps that were identified by the committee. The draft Therapeutic Review recommendations report and a document summarizing the committee's proposed updates and revisions to any existing CDA-AMC drug reimbursement recommendations (if applicable) are posted on the CDA-AMC website for partner feedback for a period of 10 business days. At this time, the draft Therapeutic Review Summary Report(s) are also posted for informational purposes.

16.3.5.2. Final Therapeutic Review Recommendations

Our organization and the chair of FMEC meet to discuss partner feedback. CDA-AMC prepares a report that includes responses to partner feedback on the recommendations and/or advice statement(s), and revisions to the proposed final statement(s) (if applicable). Once discussed and agreed upon with the chair, the report summarizing partner feedback, responses, and proposed final statements (if applicable) are presented to the expert committee. If deemed necessary by the chair of the Committee, a further discussion will be held at the next scheduled expert committee meeting. The expert committee then finalizes the recommendations and/or advice statements. A summary statement of the feedback considered will be included within the final Therapeutic Review recommendations report.

16.3.5.3. Revised Drug Reimbursement Recommendations

One of the outputs from a Therapeutic Review may be updated and revised reimbursement recommendations for drugs that have previously been reviewed through the CDA-AMC Reimbursement Review processes.

16.3.5.4. Expert Committee Recommendation Process

As part of the deliberative process for a Therapeutic Review, the expert committee will consider whether or not the results of the review suggest that any existing recommendations that were issued through 1 of our Reimbursement Reviews should be revised.

16.3.5.5. Partner Feedback on Revised Recommendations

Proposed updates and revisions to existing reimbursement recommendations will be posted for partner feedback at the time the draft Therapeutic Review recommendations are posted.

The following information will be included:

- the drug (generic and brand name where appliable) and CDA-AMC project number of the reimbursement recommendation
- the indication and date of the reimbursement recommendation
- the recommendation that may be revised as a result of the Therapeutic Review
- the updated or revised reimbursement conditions being proposed by FMEC (if applicable).

Partners will have the opportunity to provide feedback on the proposed revisions to the draft recommendations. There will be no opportunities to request reconsideration of revised reimbursement recommendations through the Therapeutic Review procedure. Only public drug programs, through the jurisdictional advisory committees, may request a reconsideration.

16.3.5.6. Consideration of Feedback From Interested Parties

Similar to feedback on the draft Therapeutic Review recommendations report, our staff will collate feedback from interested parties on any revisions to existing reimbursement recommendations. The feedback will be presented to the chair of the expert committee for consideration of revisions based on feedback from interested parties, and if deemed necessary, discussed by the committee at the next scheduled expert committee meeting for any further revisions based on feedback received.

Depending on feedback from interested parties, this could result in revisions that were not initially identified at the time of partner feedback. We will only issue a second call for partner feedback for updated and revised reimbursement recommendations when the committee's recommendation has been substantially revised following the initial round of partner feedback. Specifically, this process will apply in the following circumstances:

- the recommendation category has been changed (e.g., from a recommendation that a drug should be reimbursed with or without conditions to a recommendation that the drug should not be reimbursed)

- the reimbursement conditions have been revised to reflect a different place in therapy relative to alternative therapies (e.g., a change to the recommended sequence of therapies)
- the patient population identified in the reimbursement conditions has been substantially altered relative to the initially proposed recommendation (e.g., the population has been narrowed or expanded); in these cases, the committee will determine if an additional call for feedback from interested parties is warranted as part of the deliberations.

16.3.5.7. Finalizing Revised Reimbursement Recommendations

When the committee has determined that a previous recommendation should be updated or revised because of a Therapeutic Review, we will issue an updated recommendation and reasons. The updated and revised recommendation will be an abbreviated document containing the following key information:

- rationale for updates to the reimbursement recommendation(s)
- the recommendation(s), including any conditions (if applicable)
- a statement indicating that the revised recommendation has been issued because of a CDA-AMC Therapeutic Review
- a disclaimer indicating that the revised recommendation supersedes the previous Reimbursement Review recommendation(s) for the drug and indication of interest
- a table outlining the drug(s) and the updates or revisions to the reimbursement recommendation(s) by FMEC.

16.3.5.8. Posting Revised Reimbursement Recommendations

The revised final recommendation will contain no confidential information; therefore, manufacturers will not be asked to complete a redaction request form. Any unique information provided to CDA-AMC by impacted manufacturers, including unpublished information, is subject to being included in CDA-AMC Therapeutic Review Summary Report(s) and/or recommendation report(s) with no opportunity for redactions.

16.4. Target Timelines

Timelines are determined by CDA-AMC in consultation with the jurisdictions.

16.5. Transparency and Engagement With Interested Parties

Our organization makes every attempt to be as transparent as reasonably possible in the Therapeutic Review process. The 3 principles of transparency, as defined by the CDA-AMC, are to:

- solicit feedback from those affected by CDA-AMC reports (e.g., patient groups, health care providers, and pharmaceutical companies), whenever possible
- facilitate the ability to reproduce or update CDA-AMC reports by reporting:

- methods used to create reports
- sources searched and/or provided

- publish CDA-AMC reports in the public domain.

Therapeutic Reviews are conducted in an open and transparent fashion with input from all interested partners (i.e., public, patients, health care providers, and pharmaceutical companies) solicited to facilitate a rigorous review (refer to Table 32 for details). Our organization notifies interested parties of partner feedback opportunities by posting a notice to the Calls for Feedback web page and issuing an email to subscribers through the CDA-AMC Weekly Summary. Instructions on providing feedback are included with every notification. In the Therapeutic Review process, partner input or feedback is solicited at the following stages:

- proposed project scope
- list of included studies selected for the Clinical Review
- draft Therapeutic Review Summary Report(s) (Note: Clinical Summary and Economic Summary Reports may be posted separately, if required)
- draft Therapeutic Review recommendations report
- proposed updates and revisions to existing CDA-AMC drug reimbursement recommendations (if applicable).

Therapeutic Review Reports are posted on the CDA-AMC website for anyone to access and review, although in exceptional circumstances, embargo periods may be considered.

16.5.1. Patient Group Input

Interested patient groups are asked to complete a patient group template, available on the Calls for Feedback. Groups can contact CDA-AMC with questions.

To encourage diversity of voices and experiences, we accept patient group input from organized patient groups, but not from individual patients or caregivers. Interested individuals should either contact a relevant patient group, contact the CDA-AMC to be connected with a relevant patient group, or consider alternative input and feedback opportunities (refer to Table 32).

Once patient group input has been received, it may be summarized by our organization and sent back to the patient group(s) for comments on accuracy and completeness. The summary is incorporated into the Therapeutic Review Clinical Summary Report, with perspectives and shared experiences discussed when relevant. The completed patient group input template, as provided to CDA-AMC, is posted publicly on our website as appropriate. It is the responsibility of the patient group submitting their input and feedback to ensure no confidential patient information is included within.

Table 32: Interested Parties in CDA-AMC Therapeutic Reviews

Partner	Consultation activity

All interested parties[a]	• Provide input or feedback on:
	  ○ proposed project scope
	  ○ list of included studies selected for the clinical review
	  ○ draft Therapeutic Review Summary Report(s)
	  ○ draft Therapeutic Review recommendations report
	  ○ proposed revisions to existing CDA-AMC drug reimbursement recommendations

Pan-Canadian customers (e.g., jurisdictional advisory committees)	• Inform development of policy and research question(s) • Identify policy, reimbursement, and practice issues, as well as implementation considerations and support activities for Canadian jurisdictions
Patient groups	• Provide patient perspectives on disease and impact on quality of life • Provide first-hand experiences with treatments included in the review • Identify therapeutic issues and controversies from a patient perspective • Comment on existing CDA-AMC drug reimbursement recommendations • Provide feedback at designated stages of the process
Expert committee	• Use the CDA-AMC's Summary Report(s) and input from partners to deliberate and then develop reimbursement recommendations • Provide guidance on other issues related to reimbursement and optimal use of pharmaceutical products (e.g., identify and/or provide guidance on practice or implementation issues)
Clinical experts	• Provide context for developing research questions: ○ understanding of current clinical approach and therapeutics, natural history of disease, comparators, outcomes, interpretation of evidence, populations, and upcoming therapeutic or diagnostic trends • Identify therapeutic issues and controversies • Identify clinical practice issues that are not captured by clinical evidence review
Manufacturers	• Confirm available evidence • Provide input and feedback at designated stages of the process

CDA-AMC = Canada's Drug Agency.

[a] Includes the public and all other partners mentioned in the table.

Figure 5: Therapeutic Review Process Flow Chart

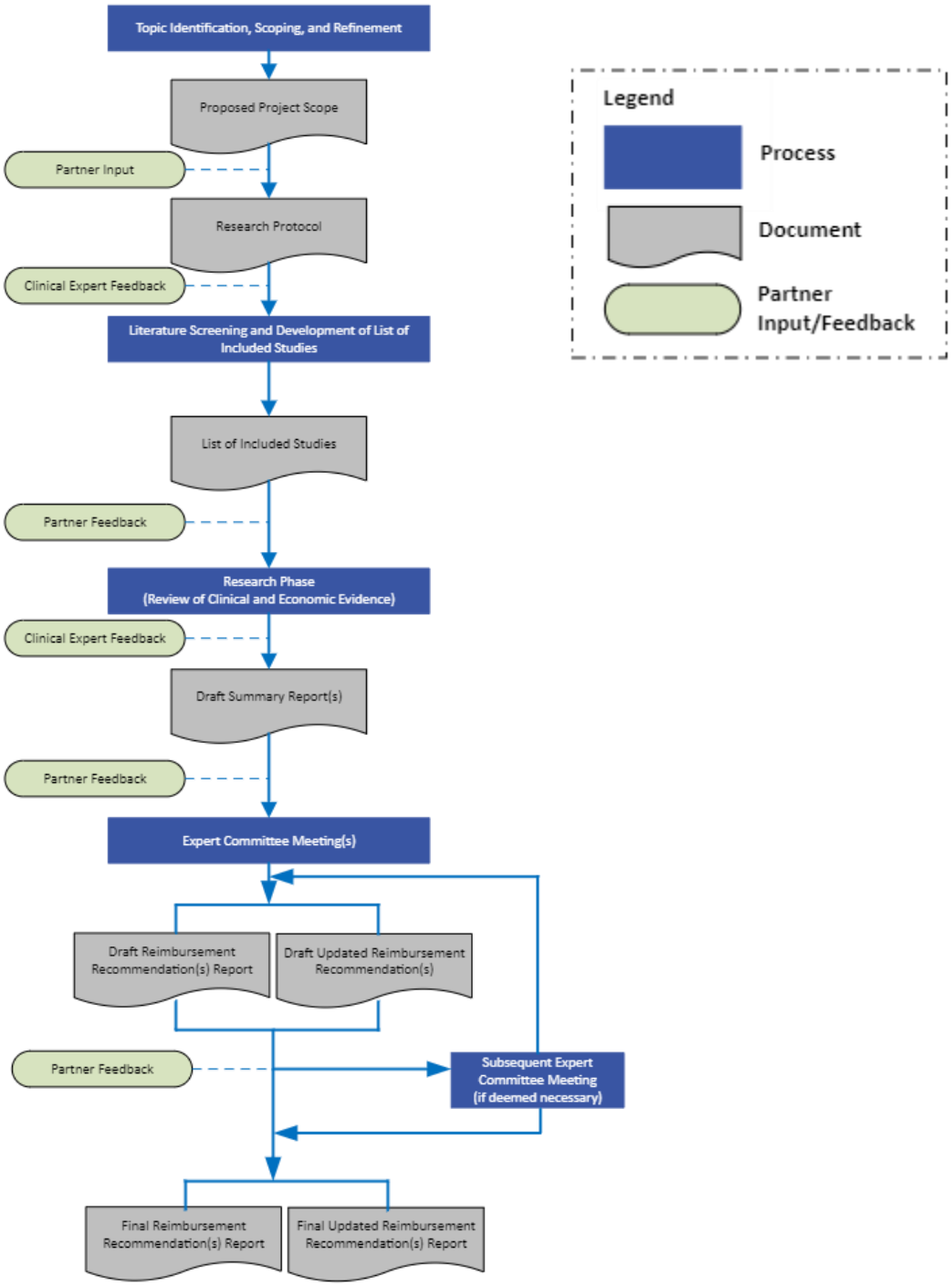


Table 33 contrasts both the therapeutic review and the streamlined review.

Table 33: Comparison of CDA-AMC Therapeutic Review and Streamlined Review

	Therapeutic Review	Streamlined Review
Requester(s)	Public drug programs, cancer agencies, or pCPA	
Prioritization	Priority established by one of the CDA-AMC advisory committees (FWG, PAG, PAC)	
Topic Selection	See key factors concerning relevance, timeliness, and potential impact within section 16.3.1	The key factors concerning relevance, timeliness, and potential impact within the therapeutic review procedures will be applied in addition to the following: • **Published meta-analyses or other published evidence:** Existing evidence assessing the clinical effectiveness (e.g., from another HTA agency). • **Utilization analyses:** Demonstration that there may be an opportunity to improve optimal use. • **Loss of exclusivity**: At least one of the drugs of interest has lost exclusivity.
Target timelines	12 to 18 months	6 to 8 months
Clinical Review	Systematic literature review with meta-analysis (if appropriate)	CDA-AMC summary and appraisal of existing published literature review(s)
Economic Evidence	Typically includes a novel pharmacoeconomic evaluation conducted as part of the CDA-AMC review	Will not include a novel pharmacoeconomic evaluation conducted as part of the CDA-AMC review, but may include the following: • a cost comparison • a pan-Canadian budget impact analysis • an economic review leveraging existing published models
Feedback from Interested Parties	Similar engagement with interested parties.	
Recommendation Procedure	Both reviews follow the same expert committee recommendation procedures.	

FWG = Formulary Working Group; PAC = Pharmaceutical Advisory Committee PAG = Provincial Advisory Group

Implementation Advice

17. Provisional Funding Algorithms

17.1. Purpose and Eligibility

The provisional funding algorithm (PFA) process is used to provide advice when the drug programs have indicated that there is a need to harmonize the place in therapy for the drug under reimbursement review relative to the alternative treatments that are currently reimbursed by the public drug programs. A PFA may impact the sequencing of treatments for the purposes of reimbursement (e.g., should reimbursing the drug under review result in a shift or a displacement of other available treatments). This process is distinct from the reimbursement review process and is offered for the purpose of assisting jurisdictions in implementing recommendations and/or making reimbursement policy decisions.

A PFA can be requested by participating provincial and/or territorial ministries of health and provincial cancer agencies through PAG during the open call for input stage of the reimbursement review process.

The development of a PFA is initiated before a reimbursement recommendation is finalized to provide public drug plans with more timely evidence to inform their decision-making. In addition, early initiation of the PFA also provides more time for meaningful engagement. If the final reimbursement recommendation for a drug under review is “do not reimburse,” the associated PFA process will be suspended.

Note: New evidence alone does not result in an update to a PFA. PFAs are only updated when new evidence has been reviewed by an expert committee (e.g., pERC, FMEC) either through a sponsor or tumour group reimbursement review (e.g., resubmission) or a public drug program–initiated non-sponsored reimbursement review. Abstracts from a recent congress or updated clinical practice guidelines do not initiate a change in a previous PFA unless previously reviewed by an expert committee.

17.2. Algorithm Process

We aim to conduct our reviews in the most efficient manner and the following processes are applied depending on the complexity of the algorithm:

- A **panel algorithm** is undertaken when the advice of clinical specialists is required to adapt an existing PFA or establish a completely new PFA. Panel algorithms will typically be initiated when 1 or more drugs may be impacted by the implementation of a new drug (e.g., shifting existing drugs to different lines of therapy).
- A **rapid algorithm** is undertaken when an expert committee (e.g., pERC or FMEC) recommendation can be directly incorporated into an existing PFA without supplemental advice from clinical specialists. The rapid algorithm process will typically be initiated in situations where the new drug will not alter the current sequence of drugs within an existing funding algorithm

(e.g., a follow-on drug within an existing line of therapy or a completely new line with no comparators).

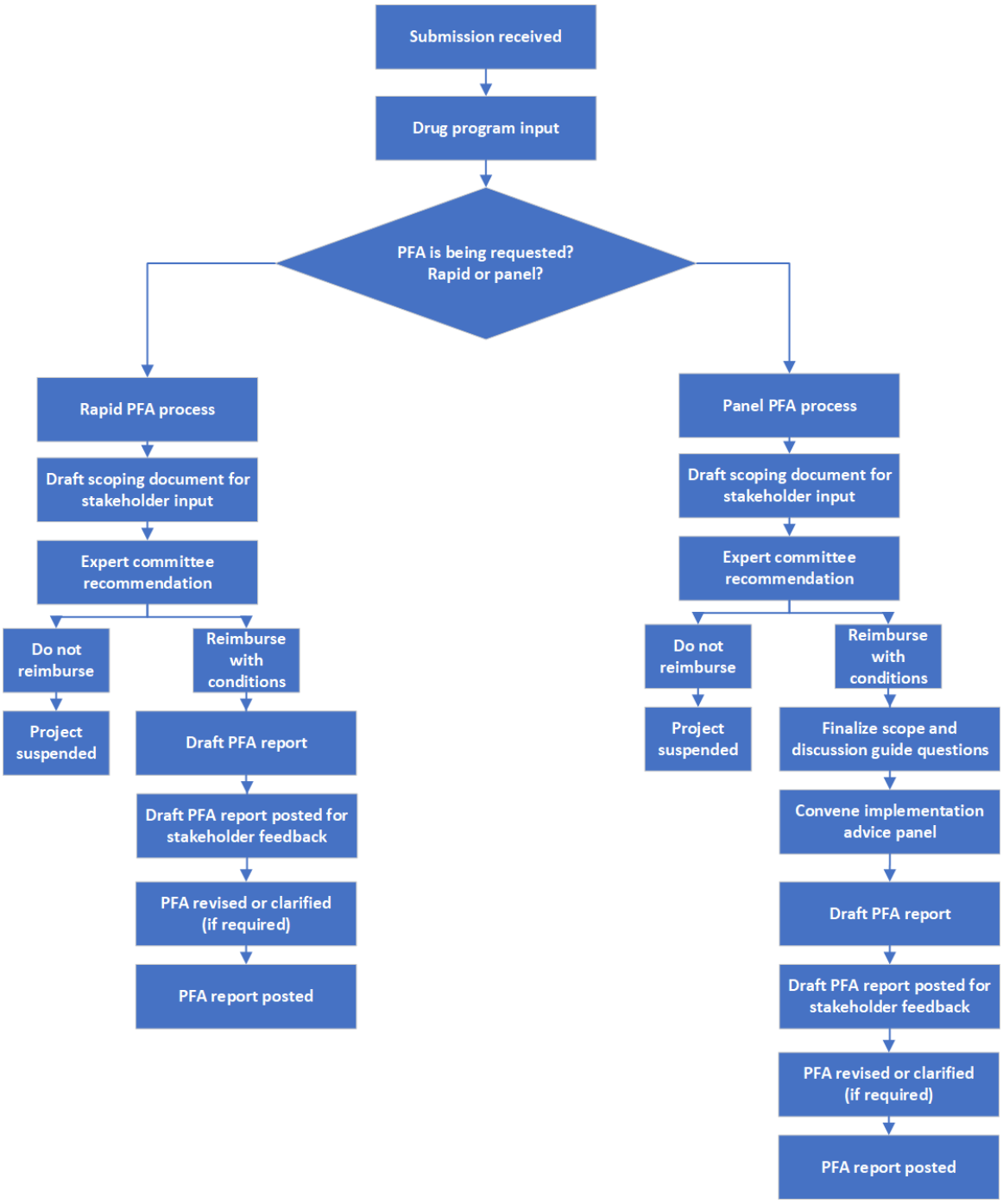
Table 34: Comparison Between Rapid and Panel Provisional Funding Algorithms

Domain	Rapid algorithm	Panel algorithm
Common rationale	The drug's place of therapy is well described in the reimbursement recommendation report.	There are outstanding questions related to the place of therapy or implementation considerations of the drug not previously addressed in the reimbursement recommendation.
Sources of information	• pERC or FMEC recommendation report • Previous PFA reports • Sponsor-submitted information related to place of therapy	• pERC or FMEC recommendation report • Previous PFA reports • Sponsor-submitted information related to place of therapy • Clinician panelists and other references identified during panel discussion
Information included in the scoping document	• Therapeutic area • Drugs likely to be implicated	• Therapeutic area • Drugs likely to be implicated • Implementation issues
Input period	35 days	35 days
Feedback period	7 days	7 days
Information included in the final report	• Pictorial and descriptive representation of the algorithm • Acknowledgement and considerations of input and feedback	• Discussion guide questions • Sources of evidence • Potential limitations • Panel discussion and advice • PAG final advice • Pictorial and descriptive representation of the algorithm • Acknowledgement and considerations of input and feedback

FMEC = Formulary Management Expert Committee; pERC = pCODR Expert Review Committee; PAG = Provincial Advisory Panel; PFA = provisional funding algorithm.

Note: A rapid algorithm may pivot to a panel algorithm following input or feedback received by CDA-AMC. Updates will be provided on our website accordingly.

Figure 5: Provisional Funding Algorithm Processes



PFA = provisional funding algorithm

17.3. Targeted Time Frames

The key targeted time frames and the status of all reviews are posted on our website. We attempt to align the timelines closely with the final recommendation report for the new drug(s). The actual timelines may vary depending on the scheduling of PAG meetings as well as the complexity of the treatment space, which may require additional discussions among the panelists and/or the need to consult additional experts (e.g., multiple panel meetings with different panel compositions, such as a panel with pathologists). These factors can impact timelines. If timelines need to be adjusted, they will be updated on our website.

17.4. Engagement With Interested Parties

Interested parties, including the industry sponsors, public drug programs, CAPCA, and patient and clinician groups, will have 35 business days to provide written input on the PFA. The sponsor whose drug is under review (i.e., who initiated the PFA) is required to submit a template with a suggested PFA. It is also recommended to include a summary of relevant previous expert committee recommendations. In addition, all sponsors (e.g., DIN holders) whose products may be directly impacted by the PFA may provide input. PAG will be engaged throughout all phases of the PFA process. CAPCA offers important input and guidance in the development of PFAs, consistent with its mandate of enhancing quality, supporting innovation, and strengthening sustainability.

Once the PFA report is drafted, all interested parties will be provided with an opportunity to review and provide comments during the feedback period of 7 business days.

Input or feedback must be provided using the appropriate templates and must not contain any confidential information (as all information included in the template will be considered disclosable). At the beginning of the input period, we will post a scoping document with the following information:

- the indication of interest
- a list of drugs that may be impacted
- implementation issues as identified by PAG (for a panel PFA only).

No requests for extensions are granted. All input or feedback, including the sponsors, public drug programs, CAPCA, and patient and clinician groups, will be considered in the PFA process and will be posted on our website for transparency.

17.5. Development of Panel Algorithms

The panelists convened to inform a panel algorithm will be comprised of clinical specialists with expertise in the diagnosis and management of the condition for which the PFA is required. The clinicians may be identified by CAPCA (e.g., clinical leads affiliated with provincial cancer agencies) or through other sources. The panel will also include a chair that is an oncologist clinician appointed by CDA-AMC in

consultation with CAPCA. While the panel chair doesn't contribute to the clinician discussion, they will work in collaboration with PAG to develop the appropriate discussion guide questions. The panel chair's role is to address the implementation issue(s), ensure the discussion remains focused, ensure the panel abides by best practices, and establish consistency among panels. A representative for PAG may attend the panel to provide the jurisdictional perspective for the meeting. All panellists will be required to comply with our Conflict-of-Interest Policy.

The panelists will be provided with details regarding the PFA, including the discussion guide questions, the existing PFA, the proposed place in therapy for the drug(s) reviewed through the reimbursement review process, and all input received.

The deliberations will be focused on addressing the specific policy questions raised by PAG. This will typically be related to understanding the implications of 1 or more new therapies on the existing sequence of treatments that are funded by the jurisdictions. The following items will be considered by the expert panelists when advising the jurisdictions on the PFA:

- unmet therapeutic need for patients (particularly those in understudied populations)
- evidence supporting a particular sequence of therapies (if available)
- clinical experience and opinion that support a particular sequence of therapies
- clinical practice guidelines
- variability across jurisdictions regarding the reimbursement status of existing treatment options
- affordability and sustainability of the health care system
- implementation considerations at the jurisdictional level.

Clinical and economic evidence to inform an optimal treatment sequence is typically limited; therefore, the clinical experience and knowledge of specialists will often form the basis of the advice offered by the panel. The rationale for the panel's proposed PFA will be documented.

In the final PFA report, the details related to the discussion guide questions, the source(s) of evidence, any potential limitations, and the panel's guidance will be published for transparency. A discussion of dissenting opinions and whether the panel advice is supported by PAG for implementation will also be included in the PFA report, as will the specialty and geographic location of the panelists.

The final report will provide both a pictorial and a descriptive representation of the algorithm.

17.6. Development of Rapid Algorithms

In consultation with PAG and starting with the materials submitted by a sponsor, we will draft a PFA using the following sources of information:

- prior pERC recommendations on all drugs that are to be considered in the PFA
- prior implementation advice and PFAs in the same therapeutic area

- drug reimbursement criteria implemented by jurisdictions at the pan-Canadian level following decisions made by consensus.

Occasionally, a rapid algorithm may pivot to a panel algorithm following receipt of input or feedback. These updates will be provided on our website.

The final report will provide both a pictorial and a descriptive representation of the algorithm.

17.7. Provisional Funding Algorithm Reports

17.7.1. Scoping Document and Call for Input

As described in section 17.5, a scoping document will be posted during the open call for input with the following information: the indication of interest, a list of drugs that may be impacted, and the implementation issues identified by PAG (for a panel PFA only).

17.7.2. Draft Provisional Algorithm Report

We will post the draft PFA report for feedback. For a panel algorithm, we will review and discuss the feedback with the chair of the implementation advice panel, who will determine if there is a need for additional discussion(s). For both panel and rapid algorithms, the feedback will be reviewed and discussed during monthly PAG meetings and draft reports will be finalized accordingly.

17.7.3. Final Provisional Algorithm Report

The final report from this process will be posted on our website. In the final PFA report of a panel algorithm, the details related to the discussion guide questions, the source(s) of evidence, any potential limitations, and the panel's guidance will be published for transparency. A discussion of dissenting opinions and whether the panel's advice is supported by PAG for implementation will be included in the PFA report.

For both panel or rapid algorithms, the final report will provide both a pictorial and a descriptive representation of the algorithm.

All eligible groups who have provided input or feedback will be acknowledged in the final algorithm report. In addition, the input and feedback will be published for transparency.

17.8. Comments on Provisional Funding Algorithms

Occasionally, interested parties may want to reach out to provide comments related to PFAs outside the open call period for input or feedback. These comments can be sent to CDA-AMC using the online form with the following information:

- the therapeutic area and publication date

- the project number
- any specific comments.

If deemed relevant, these comments will be reviewed at an upcoming PAG meeting.

18. Implementation Advice for Health Technologies

18.1. About Implementation Advice

This section outlines the procedures for implementation advice for drugs, including related testing procedures that are used to ensure their appropriate, effective, and safe use (this may include but is not limited to companion diagnostics). Procedures for implementation advice on nondrug health technologies, such as medical devices, diagnostic tests, and surgical, medical, or dental procedures, may be addressed separately through the Health Technology Expert Review Panel.

18.2. Overview of Implementation Advice

18.2.1. Eligibility

The organization provides implementation advice and support when requested by federal, provincial, and territorial ministries of health and pan-Canadian Health Organizations (e.g., pCPA and the Canadian Association of Provincial Cancer Agencies [CAPCA]). Implementation advice is intended to address relevant implementation considerations and timely policy decisions. Implementation advice is most appropriate when there are limitations or gaps with the available evidence and/or there is a need for additional consultation with subject matter experts to gather consensus regarding implementation issues.

18.2.1.1. Examples of Implementation Advice Application

Examples of when implementation advice is required may include, but are not limited to, the following:

- Federal, provincial, and territorial governments request advice to support implementation considerations in relation to:
  - testing procedures that are used to ensure the appropriate, effective, and safe use of drugs (this may include but is not limited to companion diagnostics), or
  - drugs that are nationally procured.
- Public drug programs communicate a need for time-limited advice regarding therapeutic alternatives when there is a potential or current shortage of 1 or more therapies that are standard of care in Canada.
- Public drug programs request implementation advice to support local policy decisions as a result of a recommendation from a reimbursement review (e.g., elaboration on the place of therapy of a drug [initiation, discontinuation, and prescribing criteria], advice on the appropriate use of a drug

in the Canadian context, or considerations regarding the specific groups of patients who may particularly benefit from a drug). This may involve outstanding issues that the organization's drug expert committee was unable to address due to limitations with the available evidence or the need for additional consultation with subject matter experts, such as:

- the expert committee concluded that the comparative clinical benefit of the drug has been demonstrated, but a panel of clinical specialists could be convened to specify the conditions that are essential to ensure that the treatment is reimbursed in the most appropriate manner (e.g., by considering issues such as budget constraints).
- the participating drug programs communicate that there is a need to investigate potential reimbursement conditions for patient populations that may not be addressed by the existing indications and/or recommendations (e.g., understudied populations where there may be an unmet therapeutic need).

18.2.2. Implementation Advice Panel Composition

The unique composition of each implementation advice panel (IAP) (i.e., number and type of experts) is determined based on the nature and complexity of the health technology being considered. This composition is established in consultation with our health system partners. The panel will consist of clinical experts with experience in the diagnosis and management of the condition for which the health technology under review is indicated. Additionally, the panel may include representation from areas that contribute valuable perspectives to discussions, such as health policy, ethics, and key clinician groups. Consequently, some panellists may not directly treat the indication(s) impacted by the drug or technology under review. A panel chair will be appointed.

Potential panel experts will be identified and, whenever possible, representation from across Canada will be sought. While the area of expertise and the region in which the panel experts practice will be disclosed, the identities of the panel experts will be confidential.

The organization will apply its current conflict of interest policy and all panellists will be required to provide a completed conflict of interest declaration.

18.3. Targeted Time Frames and Tracking

The phases of the implementation advice process can be found in Table 35. The key milestones for the implementation advice process can be found in Table 36. In situations where the RFA is urgent, timelines may be expedited (i.e., rapid IAP). Timelines may vary depending on the panellists' availability and prescheduled advisory and expert committee meetings of the organization.

Targeted time frames and the status of IAPs are posted on the organization's website. Interested parties, including manufacturers with health technologies that are within the scope of an IAP, will be notified though the Weekly Summary email and/or directly by the organization when applicable.

Table 36 and Table 37 provide an overview of how the standard IAP process may be adapted in rapid IAP circumstances. In situations where publicly available evidence is limited (e.g., before a Health Canada Notice of Compliance), an industry sponsor may be engaged. Section 18.7 outlines additional procedural requirements for when published evidence is limited and the organization engages with the manufacturer to provide the most relevant and up-to-date data and/or evidence.

Table 35: Phases of the Implementation Advice Process

Phase of process	Key tasks
Project initiation	Request received
	Lead jurisdiction identified, review team assembled, and relevant manufacturer(s) of involved technology or technologies notified when relevant
Scoping phase	Scope of implementation advice process reviewed with involved health system partners (e.g., federal, provincial, and/or territorial governments) and scoping document posted
	Input period for scoping document
Deliberation and draft advice report	Draft summary of evidence prepared, panel prepared, and meeting convened
	Draft implementation advice report prepared
Feedback phase	Feedback period for draft implementation advice report; this may include, when relevant, panellists; representatives of federal, provincial, and territorial governments and their relevant agencies; pan-Canadian health organizations; manufacturer(s)
Final report	Feedback reviewed and considered by the organization and panel
	Implementation advice report finalized
	Final report copy-edited and formatted for posting
	Final report posted on the organization's website

Table 36: Implementation Advice Process Key Milestones

Phase of process	Key milestones	Standard IAP	Rapid IAP
Project initiation	Request received and review process initiated	Day 1	Day 1
	Relevant manufacturer(s) of involved technology or technologies notified when relevant[a]	Day 4	Day 4
Scoping phase	Scoping document posted and open for input	Day 10	NA[b]
	Input period closed	Day 20	NA
Implementation advice panel	Panel meeting convened	Day 25	Day 20
Feedback phase	Draft implementation advice report open for feedback; this may include, when relevant, panellists; representatives of federal, provincial, and territorial governments and their relevant agencies; pan-Canadian health organizations; manufacturer(s)[a,c]	Day 43	Day 26[c]
	Feedback period closed	Day 53	Day 28
Final report	Final report posted on the organization's website	Day 75[d]	Day 50[d]

IAP = implementation advice panel; NA = not applicable.

Note: Days refer to business days.

[a] Manufacturers with health technologies that are included in the scope of the IAP may be contacted by the organization. Additional evidence to inform the IAP are not required from manufacturer(s), although additional evidence will be considered. In most cases, should manufacturers provide additional information, there will be no opportunity for redactions. In situations where publicly available evidence is not available (e.g., before receiving market authorization from Health Canada or after receiving market authorization from Health Canada [i.e., pre-Notice of Compliance and post-Notice of Compliance, respectively]), the organization will contact the manufacturer for additional information and there will be opportunity for redactions. (Refer to Table 37 and section 18.7 for more information).

[b] For rapid IAPs, the organization will not issue open calls for input or feedback given the time-sensitive nature of these requests and given that advice provided may be time-limited. Input is only sought for single technology rapid IAPs where the only data available are from the manufacturer. The manufacturer will have 5 business days to provide written input (refer to section 18.7).

[c] This timeline is expedited with rapid IAPs. Feedback from panellists and representatives of federal, provincial, and territorial governments and relevant pan-Canadian Health Organizations will comprise the core feedback. Draft reports will only be shared with manufacturers for feedback in the case of a single health technology IAP where data are only available from the manufacturer. In these cases, the draft report will be shared and the manufacturer will have 2 business days to provide comments (refer to section 18.7).

[d] This is the total business days from project initiation to completion. Actual timelines may depend on panel availability and may also be extended if there is a need for an additional panel meeting.

18.4. Engagement With Interested Parties

Interested parties will be notified though the Weekly Summary email of active IAPs. Opportunities for input and feedback can be found on the organization's website in Open Calls for Input and Feedback.

A scoping document with the following information will be posted:

- the topic of interest for which implementation advice will be developed
- the health technologies, and the respective indication(s) if applicable, that may be impacted by the implementation advice report
- the target dates for providing input and feedback.

Upon notification that implementation advice is being developed, all interested parties, including manufacturers with products that fall within the scope of implementation advice, will have 10 business days to provide written input regarding their perspective on the issues raised by the jurisdictions. This input must be submitted using the template provided and must not contain any confidential information (all information included in the template will be considered disclosable). No requests for extensions will be granted.

18.4.1. Manufacturers

All manufacturers (e.g., DIN holders) with health technologies that are within scope of an IAP will be permitted to provide input and feedback through the open call for feedback process.

18.4.2. Patient and Clinician Group Engagement

For IAPs related to a health technology review or reimbursement review, the panellists will receive copies of any input received during the open call for input from patient and clinician groups, as well as from laboratories and imaging centres whose resources may be affected by the health technology, when applicable. The input received will be summarized in the report. Patient and clinician groups, as well as laboratories and imaging centres whose resources may be impacted by the health technology, are encouraged to focus their input on the perspectives and issues of patients and/or their caregivers related to the condition for which the health technology and any relevant testing considerations under review are indicated. This includes assessing the impact and unmet needs of current therapy and the treatment outcomes of greatest importance, addressing equity and accessibility issues, and specifying the expectations for the health technology under review. This information will provide important context during the panel's deliberations.

18.4.3. Drug Program Engagement

To ensure that implementation considerations are clearly addressed by the IAP and to help expedite the overall process, consultation and feedback will be sought from federal, provincial, and territorial governments, as well as relevant pan-Canadian health organizations during the review, as deemed appropriate. Drug programs may also observe panel meetings and provide feedback on draft implementation advice reports.

18.5. Deliberations and Implementation Advice Report

18.5.1. Evidence Review

If applicable, the organization will summarize and conduct an appraisal of the evidence available to address the implementation questions. The approach and evidence sources may vary depending on the implementation issue or considerations identified by the requester. If a review is necessary, the strengths and limitations (internal and external validity) of the evidence retrieved will be documented with respect to matters such as, but not limited to, relevance, credibility, and methodology.

Evidence informing the IAP may come from publicly available sources, including reports by the organization, scientific publications, international HTA organizations, product monographs, and regulatory reviews conducted by international regulatory bodies, as well as evidence provided by a manufacturer.

For any evidence provided by the manufacturer, the organization will summarize and conduct an appraisal of the evidence.

If applicable, a summary of the evidence review will be incorporated in the implementation advice report or document.

18.5.2. Preparing and Briefing Panel Members

Before convening the IAP, panel members will be provided with a brief for review that will typically include, but not be limited to, the following materials:

- the specific implementation and/or policy question(s) raised by the requesting health system partner and/or jurisdictions for the panel
- evidence review
- Input when applicable, such as a summary of patient input, clinician input, and input from laboratories and imaging centres whose resources may be impacted by the health technology for IAPs related to a health technology or reimbursement review
- draft or final product monograph(s) for any drug(s) under review
- key clinical studies (e.g., manuscripts and/or clinical study reports)
- any manufacturer input on the implementation issues (where applicable)
- manufacturer-provided table of studies (where applicable).

In situations where a manufacturer provides materials to the organization, the panellists will also be provided with this information.

18.5.3. Convening the IAP

The organization will convene the IAP. Attendance at any IAP meeting(s) will typically be limited to the panel experts and/or specialists, key agency staff (i.e., review team members), and relevant health system partner representatives (i.e., the public drug programs; federal, provincial, and territorial ministries of health; applicable pan-Canadian health organizations). Manufacturer(s) will not be able to attend the panel meetings at this time. Representatives from INESSS and/or INESSS expert committee members may also attend the IAP meetings.

18.5.4. Panel Deliberation Considerations

The following items may be considered by the panellists as part of the deliberations, based on availability and appropriateness:

- clinical evidence supporting the effectiveness of particular health technologies, their effectiveness with specific populations, or objective measures to determine treatment success or failure in specific populations, and so forth
- clinical experience and opinion that support the use of particular therapies or their most appropriate use or dosing regimens for specific populations, and so forth
- clinical practice guidelines
- patient, caregiver, clinician, and/or impacted laboratory and/or imaging centre perspectives related to the condition for which the drug or technology under review is indicated, such as the impact and unmet needs of current therapy, the treatment outcomes of greatest importance, and the expectations for the drug under review (as identified in the input submitted by patient groups)
- the reimbursement status of the treatment option(s) across jurisdictions
- the reimbursement status of relevant testing considerations
- implementation considerations at the jurisdictional level
- limitations of available evidence and literature.

Clinical evidence to inform the panel deliberations may be limited; therefore, expert opinion will also inform the advice offered by the panel. In more complex cases, more than 1 panel meeting may be required to support full deliberations. The rationale for the panel's advice will be provided and documented in the report.

18.5.5. Draft Implementation Advice Report

The organization will draft preliminary implementation advice in the form of a report that will be based on the panel's discussions and conclusions. The rationale for the panel's advice will also be documented in the draft report, along with the summary of evidence. The initial draft report will be provided to all panel members for their review and feedback. When appropriate, feedback on the initial draft will also be

obtained from applicable representatives of federal, provincial, and territorial governments and relevant pan-Canadian health organizations.

The organization will review and discuss any feedback received on the preliminary draft with the chair of the implementation advice panel, who will determine if there is a need to reconvene the panel to discuss feedback that may warrant revisions to the initial draft of the report.

18.5.5.1. Feedback on Draft Implementation Advice Report

Following review by the panel and by federal, provincial, and territorial ministries of health, the draft implementation advice report will be posted for feedback. The call for feedback will be open for 10 business days. No requests for extensions will be granted. Comments must be provided using the template provided and must not contain any confidential information (all information included in the submitted template will be considered disclosable). The organization will prepare responses to any comments submitted by manufacturers, which will be provided to the manufacturer(s) at the same time as the final implementation advice report.

18.5.6. Final Implementation Advice Report

All feedback received through the feedback process will be discussed with the panel chair, who will determine if there is a need to reconvene the panel for additional meeting(s) to discuss and revise the implementation advice report. After this process, the final report will be posted. There will be no confidential information included in the implementation advice report; as such, manufacturers and other interested parties will not be able to request any redactions.

18.6. Adaptations for Rapid Implementation Advice Procedures

Table 37: Key Differences Rapid and Standard Implementation Advice Process

Standard Phases and Key Tasks of Implementation Advice Process	Phases and Key Tasks of Rapid IAPs	IAP status
Project initiation		
Request received and review process initiated	Market Authorization Status • Implementation advice can be initiated prior to a health technology receiving market authorization from Health Canada or after receiving market authorization from Health Canada (i.e., pre-Notice of Compliance [NOC] and post-NOC, respectively). • Reviews may include evidence for use of drug(s) that may not have a Health Canada Notice of Compliance (NOC) or	Consistent with standard IAP

Standard Phases and Key Tasks of Implementation Advice Process	Phases and Key Tasks of Rapid IAPs	IAP status
	Notice of Compliance with Conditions (NOC/c) for the indication being reviewed.	
Relevant manufacturer(s) of involved technology/technologies notified when relevant	Single Technology IAPs Where Data are only Available from the Manufacturer (e.g., Nationally Procured Drug Product Reviews): The organization notifies the manufacturer of the technology under review. • Pharmaceutical industry manufacturers are typically the DIN holders for the drug being filed for review; however, it could be another manufacturer, supplier, or entity recruited by the manufacturer or the supplier. • Additional procedural requirements and considerations apply (e.g., pre-submission meetings, required manufacturer documentation, input timelines, etc.). • The organization may temporarily suspend the review in accordance with section 12. If the sponsor voluntarily withdraws from the process, the organization may continue with the review but will not use any information that has been filed by the sponsor in confidence. It may be noted on the organization's website that the manufacturer voluntarily withdrew from the process. Therapeutic Alternatives IAPs: As these IAPs are initiated by F/P/Ts, no documentation will be required from industry manufacturer(s), although additional information provided from them may be considered. Should manufacturers wish to provide additional information, there will be no opportunity for redactions.	Potential adaptations for rapid IAP
Scoping phase		
Input period for scoping document	Open calls for input are not issued given time-sensitivity of these IAPs and that advice provided may be time-limited (e.g., for the period of a supply shortage).	Potential adaptations for rapid IAP

Standard Phases and Key Tasks of Implementation Advice Process	Phases and Key Tasks of Rapid IAPs	IAP status
	Single Technology IAPs Where Data are only Available from the Manufacturer: The manufacturer will have 5 business days to provide written input. During the review phase, the organization may request from the manufacturer any additional information and clarification required to complete the review.	
Implementation advice panel		
Panel meeting convened	Consistent with Standard Implementation Advice Panel.	Consistent with standard IAP
Feedback phase		
Feedback period for draft implementation advice report: • panelists • F/P/T representatives and relevant pCHOs	Consistent with Standard Implementation Advice Panel.	Consistent with standard IAP
• Manufacturer(s) when relevant (including redaction requests in select Rapid IAPs, only as noted)	• Therapeutic Alternatives IAPs: Draft reports will not be shared with manufacturers. • Single Technology IAPs Where Data are only Available from the Manufacturer: Draft reports will be provided to the manufacturer for review and comment. The manufacturer will have 2 business days to provide comments.	Potential adaptations for rapid IAP
Final report		
Implementation advice report finalized	• Single Technology IAPs Where Data are only Available from the Manufacturer: Manufacturer review and validation of redactions prior to posting.	Potential adaptations for rapid IAP
Final report posted on the organization's website	Consistent with Standard Implementation Advice Panel.	Consistent with standard IAP

18.7. Additional Procedural Requirements for Rapid IAPs Involving Single Technology Reviews Where Data Are Only Available From the Manufacturer

In the case of Rapid IAPs involving a single technology for which related data are only available from the manufacturer (e.g., Nationally Procured Drug Products Reviews involving a drug that has not yet received market authorization from Health Canada), some unique and additional procedural requirements apply as outlined here. Any manufacturers with questions about this process should contact CDA-AMC.

18.7.1. Eligibility

18.7.1.1. Drug Eligibility

Eligibility for these Rapid IAPs will be determined by the organization in consultation with federal, provincial, and territorial governments. Manufacturers with eligible products will be contacted.

18.7.1.2. Market Authorization Status

Reviews can be initiated prior to receiving market authorization from Health Canada or after receiving market authorization from Health Canada (i.e., prior to Notice of Compliance [NOC] and after NOC has been received, respectively).

18.7.1.3. Manufacturer Eligibility

Pharmaceutical industry manufacturers are typically the Drug Identification Number (or DIN) holders for the drug being filed for review; however, it could be another manufacturer, supplier, or entity recruited by the manufacturer or the supplier.

18.7.1.4. Declining to Participate

If a manufacturer declines to participate in the review process (e.g., failure to provide the required documentation), the organization may continue with the review based on publicly available information. The manufacturer may not have the opportunity to review and comment on the draft report prior to publication.

18.7.2. Meetings with CDA-AMC

Meetings may be offered in the same manner as described in section 7.1.3.

18.7.3. Required Documentation

Table 38 summarizes the documentation that is required for the review of nationally procured drug products. Details concerning each of the requirements are provided in section 6.

Table 38: Required Documents for Review of Nationally Procured Drug Products

Section	Specific items and criteria
General information	Draft and final product monograph
	Completed declaration letter template
Health Canada documentation	Table of Clarimails or Clarifaxes (as soon as available)
Efficacy, effectiveness, and safety information	Results for pivotal and supportive clinical studies
	Common Technical Document sections 2.5, 2.7.3, 2.7.4, and 5.2 (if applicable)
	Clinical study reports for pivotal and key studies (if applicable)
	Table of studies

18.7.4. Engagement With Interested Parties

18.7.4.1. Manufacturer Engagement

Once the request for implementation advice has been received, the manufacturer of the drug under review will be notified. The manufacturer will have 5 business days to provide written input regarding the implementation issues. This input must be submitted using the template provided by CDA-AMC and must not contain any confidential information (all information included in the template will be considered disclosable).

The manufacturer will be provided with the opportunity to review and comment on the draft implementation advice report. During the review phase, additional information and clarification may be required from the manufacturer to complete the review. These requests will be provided in writing, and the manufacturer is encouraged to respond in a timely manner to avoid potential delays in the review timeline.

18.7.4.2. Patient and Clinical Group Engagement

The organization recognizes the value of patient and clinician perspectives in reviews of medical procedures, devices, and drugs. Patients' and clinicians' perspectives contribute to the scientific and democratic legitimacy of the work. The organization strives to engage with patient and clinician groups during streamlined panel deliberations.

18.7.4.3. Federal, Provincial, and Territorial Governments

The organization may consult and seek feedback from the federal, provincial, and territorial governments and their agencies.

18.7.5. Health Canada Information Sharing

IAPs involving drugs that are still undergoing NOC review by Health Canada (e.g., reviews of nationally procured drug products) or involving a single technology where data is directly required from the

manufacturer will be eligible for the information sharing process as described in section 1.1. This permits Health Canada and the organization to exchange information regarding the drug(s) under review. To help avoid delays in the review process, manufacturers are strongly encouraged to participate in this process.

18.7.6. Filing and Screening Procedure

By filing documentation with the organization and participating in the review process, the manufacturer consents to be bound by the terms and conditions specified in this document and all provisions regarding the withdrawal from the process. Consent to the terms and conditions contained herein cannot be revoked by the manufacturer at any time during or after the review processes.

18.7.6.1. Filing Documentation

Manufacturers must be registered with the Pharmaceutical Submissions SharePoint before filing the required documents. For detailed information on how to register, please consult the Pharmaceutical Submissions Sharepoint Site – Setup Guide.

18.7.6.2. Document Screening

There is no formal document screening process for nationally procured drug products drugs. Materials will be reviewed as they are received and the manufacturer may be contacted for additional material or clarification, if required.

18.7.6.3. Finalized Information for Reviews Conducted on a Pre-NOC Basis

For reviews that are initiated on a pre-NOC basis, some requirements will be outstanding or not finalized at the time that the initial documentation is filed with the organization (e.g., product monograph). The manufacturer must provide all outstanding and/or finalized requirements to the organization as soon as they are available. The organization will assess the finalized information upon receiving it. Depending on the nature and extent of changes to the information compared with what was originally filed, the organization will determine the timelines required to review the information and incorporate it into the report. This could result in an extension of review timelines. The manufacturer will be notified of any revisions to the anticipated timelines.

18.7.7. Draft Implementation Advice Report

18.7.7.1. Sponsor Comments

The draft implementation advice report is provided to the sponsor for review and comment. The sponsor will have 2 business days to provide their comments. This input must be provided using a template provided and must not contain any confidential information (all information included will be considered disclosable). The organization may also obtain feedback from representatives of federal, provincial, and territorial governments and agencies. The organization will review and discuss the feedback with the

panelists and the guidance report will be revised, as required. There will be no further opportunities to formally comment on the implementation advice report prior to issuing the final report.

18.7.7.2. Redaction Requests

Before posting on the organization website, sponsors are responsible for identifying and requesting the redaction of any confidential information supplied by the sponsor that may have been included in the final implementation advice report. If the sponsor requests that confidential information be redacted from the final implementation advice report, the organization will redact the confidential information in accordance with the Confidentiality Guidelines described in Appendix 1.

Sponsors are asked to identify any confidential information using the identification of confidential information template provided. All requests for redactions must be accompanied by a clearly stated rationale. Sponsors must submit the completed form via the Pharmaceutical Submissions Sharepoint site by the pre-specified date and time (typically 4:00 p.m. Eastern Time 2 business days after the draft implementation advice report was issued to the sponsor).

18.7.8. Final Implementation Advice Report

18.7.8.1. Posting Final Implementation Advice Report

The final report from this process will be posted on the organization website. Prior to posting, the manufacturer will be requested to review and validate any redactions that were requested on the draft implementation advice report.

18.7.8.2. Validation of Redactions

The sponsor will have 1 business day to review and validate the redactions in the final implementation advice report. If the sponsor expresses disagreement regarding redactions, the organization may require additional time to resolve the disagreement in consultation with the sponsor. This additional time could delay the timeline for posting the final implementation advice report.

18.7.8.3. Temporary Suspension and Withdrawal

The organization may temporarily suspend the review in accordance with section 12. If the sponsor voluntarily withdraws from the process, the organization may continue with the review but will not use any information that has been filed by the sponsor in confidence. It may be noted on the organization website that the manufacturer voluntarily withdrew from the process.

Appendix 1: Confidentiality Guidelines

To further enhance and strengthen the transparency of the CDA-AMC reimbursement review processes by minimizing the volume of redactions in reports and recommendations, CDA-AMC has developed these confidentiality guidelines. These guidelines will help ensure appropriate steps and procedures are in place so that the disclosure of information obtained through the reimbursement review processes is handled and managed in a consistent manner.

Together with the Procedures for Reimbursement Reviews, the confidentiality guidelines provide clarity to CDA-AMC and sponsors on how to appropriately protect and disclose information, allowing for a reimbursement review process that is transparent and accountable. CDA-AMC complies with these confidentiality guidelines when handling confidential information related to the reimbursement review processes. By filing an application or by supplying other information to CDA-AMC for a filed application, each sponsor consents to complying with the requirements of these confidentiality guidelines and establishes an agreement between CDA-AMC and the sponsor on its application.

A. Definition of Confidential Information

Sponsor-supplied information that will be treated by CDA-AMC as confidential includes proprietary scientific, technical, or commercial information about a manufacturer's business or a manufacturer's product received through the exchange of information as part of CDA-AMC's reimbursement review processes, but does not include information that:

- is or becomes available to the public other than because of a breach of the procedures contained herein (note that information available to the general public includes but is not limited to published articles, drug prices, product monographs, clinical study information available from regulatory agency reports, other HTA agency reports and recommendations, and www.clinicaltrials.gov)
- a third party (who is not under any obligation as to confidentiality or non-disclosure) rightfully discloses to any authorized recipient (as described in these guidelines) without restriction as to its use or disclosure
- is provided to an authorized recipient (as described in these guidelines) without restriction as to its use, and the authorized recipient may disclose in accordance with its respective statutory requirements
- information that is identified as not redactable in Table 39.

Sponsors must clearly identify any confidential information and provide the rationale for requesting the redaction of that information.

Table 39 provides sponsors with guidance regarding what information that has been included in an application will and will not be considered redactable by CDA-AMC. Please note that the list provided in Table 39 is intended as general guidance and exceptions may be considered on a case-by-case basis

(in favour or against the redaction of information included in the CDA-AMC reported). Table 40 outlines minimum reporting requirements for situations where redaction may be permissible.

Table 39: Guidance on Information That Is and Is Not Redactable

Item	Redactable	Rationale
General Information		
Changes to the indication during the review of a submission filed on a pre-NOC basis.	Not redacted	The indication and/or sponsor's requested reimbursement conditions will not be considered confidential by CDA-AMC once this information has been posted on the CDA-AMC website (e.g., at the time of issuing the call for input). If the indication and/or sponsor's requested reimbursement conditions are revised during the review of a submission filed on a pre-NOC basis, the originally filed information will not be considered confidential by CDA-AMC once it has been published on the CDA-AMC website.
Changes to the dosing, dosage forms, or dosage strengths during the review of a submission filed on a pre-NOC basis.	Redactable	Changes relating to the recommended dosing, dosage forms, or dosage strengths (e.g., strengths filed for review on a pre-NOC basis but not approved by Health Canada) may be considered redactable if the information is not publicly available.
Clinical Data		
Methods used to conduct a study or to analyze data from a study.	Not redacted	Methods information is required to understand how model inputs are derived.
Clinical data that are available in the public domain.	Not redacted	Information that is publicly available is not considered confidential information by CDA-AMC.

Item	Redactable	Rationale
Clinical data not yet in the public domain but either: awaiting publication, including in a journal OR will be released into the public domain by regulatory authorities	Not redacted	To avoid redaction of data that will subsequently be available and when publishing in committee papers will not jeopardise publication elsewhere. The International Committee of Medical Journal Editors (ICMJE) recommendations on overlapping publications state that it 'does not consider results or data contained in assessment reports published by health technology assessment agencies, medical regulators, medical device regulators, or other regulatory agencies to be duplicate publication'.
Clinical data that has not been made publicly available and for which there is no plan for the data to become publicly available.	Redactable, except for minimum reporting requirements.	In recognition that there will be unpublished clinical data that will be confidential. However, to allow transparent reporting of decision making, CDA-AMC has outlined minimum reporting requirements for data which is likely to be fundamental to committee decision making (refer to Table 40). Clinical data should be treated as clinical data without a publication plan if: there is clinical data awaiting first public presentation at a congress that is scheduled to take place after documentation from CDA-AMC would be released to the public, and this data is not awaiting publication in a journal or within marketing authorisation documentation.
Data from real-world evidence studies that has not been made publicly available and for which there is no plan for the data to become publicly available.	Redactable (if collected by company then minimum summary information should be provided). The confidentiality requirements of third-party sources of data will be adhered to.	See the above rationale for clinical data that has not been made publicly available and for which there is no publication plan.

Item	Redactable	Rationale
Company's indirect comparison that has not been made publicly available and for which there is no plan for the data to become publicly available	Redactable, except for minimum summary information.	Assessing the benefit of a technology compared with its comparators and the uncertainty around these comparisons is fundamental to committee decision making. CDA-AMC has outlined the minimum reporting requirements for indirect comparisons outcomes to allow transparent reporting of committee decision making (refer to Table 40).
Critical appraisal of clinical studies and indirect comparisons (for example, of the validity of methodology and assessment of bias and uncertainty).	Not redacted	Critical appraisal is not considered to be confidential information and will not be redacted. This applies to critical appraisals carried out by both the sponsor and CDA-AMC.
Data derived from clinical opinion.	Not redacted	Clinical opinion may vary, and it is vital to have transparent discussion. This includes the outcome of expert elicitation. Clinical expert opinion is not considered to be confidential information and will not be redacted.
References	Not redacted	Referencing is required to understand where inputs and assumptions are derived and does not predicate inputs that are considered confidential.
Pharmacoeconomic Evaluation		
Description of methods used to conduct the economic evaluation.	Not redacted	Methods of economic evaluations are not considered confidential, as they are required to understand what was submitted.

Item	Redactable	Rationale
Weighted distribution of comparator and/or subsequent treatments.	Not redacted	Methods of economic evaluations are not considered confidential. The definition of the comparator is critical to understand the results of the economic model. Where distributions/data are based on public sources of information or expert opinion, this information will not be redacted. If the input(s) is based on clinical trial information that is not publicly available, then this information is redactable. If the input(s) is based on alternate data source (e.g., claims data), AND no supporting reference is provided, the input(s) are not redactable. Evidence of the use of commercial in confidence information must be provided to CDA-AMC (i.e., a detailed technical report outlining the data used and methods to derive the inputs) to be considered redactable.
Clinical inputs that are in the public domain.	Not redacted	Information that is publicly available is not considered confidential information by CDA-AMC.
Data from clinical studies that are not in the public domain.	Redactable	If the data are from clinical studies and the results are not in the public domain, then this information is redactable.
Data that are not in the public domain but are derived from expert opinion or sponsor assumptions (e.g., the data are not from unpublished clinical studies).	Not redacted	If the input(s) is based on expert opinion or assumption, then it is not considered redactable. Any information that is listed as “assumption” or “data on file” will not be redacted unless a detailed technical report has been provided for this information to indicate the derivation methods of the input(s).
Submitted price for the drug under review.	Not redacted	CDA-AMC does not accept confidential submitted prices for applications filed for review through its reimbursement review processes. The submitted price is disclosed in all applicable CDA-AMC reports.

Item	Redactable	Rationale
Prices for comparators and companion diagnostic testing (if applicable).	Not redacted	CDA-AMC does not accept confidential submitted prices for applications filed for review through its reimbursement review processes. The prices of comparators and/or companion diagnostic testing are disclosed in all applicable CDA-AMC reports.
Results in the sponsor's economic evaluation (e.g., ICER, total or incremental LYs, total or incremental QALYs, total or incremental costs).	Not redacted	Results from the sponsor's economic evaluation are not considered to be confidential and will not be redacted. There may be rare situations where reporting of results may result in the ability to back-calculate confidential information exactly (e.g., when deterministic results are used). The burden of proof is on the sponsor to demonstrate how this can be done (to be included with the request for redaction).
CDA-AMC critical appraisal of the sponsor's economic evaluation.	Not redacted	CDA-AMC appraisal of the methods and data used in the sponsor's pharmacoeconomic evaluation is not redacted.
CDA-AMC reanalyses of the economic evaluation (e.g., ICER, total or incremental LYs, total or incremental QALYs, total or incremental costs).	Not redacted	Results of the economic model, including CDA-AMC reanalyses, are not considered to be confidential and will not be redacted.
Model output (e.g., disaggregated health state, cost category results, health state distribution over time, etc.).	Not redacted	Results of the model, sponsor's results and CDA-AMC reanalyses are not redacted. There may be exception situations where reporting of results may result in the ability to back-calculate confidential information exactly (when deterministic results are used). The burden of proof is on the sponsor to demonstrate how this can be done (to be included with the request for redaction).

Item	Redactable	Rationale
Assumptions which are not based on empirical data.	Not redacted	The expert committee's discussion on validity of assumptions needs to be described transparently.
References	Not redacted	Referencing is required to understand where inputs and assumptions are derived and does not predicate inputs that are considered confidential.
Budget Impact Analysis		
Description of design of the budget impact analysis.	Not redacted	A description of the methods is required to understand the model.
Estimates for population size, market share, displacement of comparators, and resource assumptions that are based on published information.	Not redacted	Information that is publicly available is not considered confidential information by CDA-AMC.
Estimates for population size, market share, displacement of comparators, and resource assumptions that are based on unpublished information from the following sources: Expert opinion Assumption that is not supported by evidence (e.g., where no reference is provided, or stated as data on file with no reference provided).	Not redacted	Methods of budget impact analyses are not considered confidential. They are required to understand what is being conducted and measured.
Estimates for population size, market share, displacement of comparators, and resource assumptions that are based on unpublished information from market research obtained from a third party that cannot be publicly disclosed due to licensing agreements. This is exclusive of expert opinion.	Redactable	CDA-AMC considers information from these sources as confidential information and will redact when requested by the sponsor. However, to be considered redactable the sponsor must provide CDA-AMC with evidence that the information is commercial in confidence information (e.g., a detailed technical report outlining the data used and methods used to derive the inputs)

Item	Redactable	Rationale
Sponsor's estimated budget impact (yearly and 3-year total).	Not redacted	Results from the sponsor's budget impact analysis are not considered to be confidential and will not be redacted. There may be rare situations where reporting of results may result in the ability to back-calculate confidential information exactly (e.g., when deterministic results are used). The burden of proof is on the sponsor to demonstrate how this can be done (to be included with the request for redaction).
CDA-AMC critical appraisal of the budget impact analysis.	Not redacted	CDA-AMC critical appraisal of the methods and data used in the pharmacoeconomic submission is not redacted.
CDA-AMC estimated budget impact (yearly and 3-year total).	Not redacted	CDA-AMC reanalyses are not considered to be confidential and will not be redacted.
Data which is commercially sensitive or allows back-calculation of data which is commercially sensitive.	May be redactable	Please see guidance on how this may be applied in Table 23.
References	Not redacted	Referencing is required to understand where inputs and assumptions are derived and does not predicate inputs that are considered confidential.
Time-Limited Recommendations		
Evidence-generation requirements for conditional regulatory approvals (i.e., NOC/c) described within the Qualifying Notice from Health Canada.	Not redacted	This information is required to ensure that interested parties, including patients, understand: the rationale for the time-limited recommendation the type of evidence that will be generated to address the uncertainty the time frame for generating and submitting the evidence.

The purpose of Table 23 is to outline the information which is fundamental to the expert committee's decision making and the minimum reporting requirements that are needed to ensure the reimbursement review process is transparent.

- **Standard reporting requirements:** These refer to information that will not be redacted whenever possible.
- **Minimum reporting requirements:** These should be used when there is a demonstrated risk to the company of releasing data specified in the standard reporting column. When these minimum reporting requirements list a descriptive summary of the data, this should be presented in addition to the data which is highlighted as confidential by the sponsor.

Table 40: Standard Reporting and Minimum Reporting Requirements

Standard reporting requirements	Minimum reporting requirements
Baseline and patient characteristics of trial populations that will be subject to disclosure by Health Canada.	This data for the whole trial population should be reported in full because it is expected to be published within marketing authorization documentation.
• Baseline and patient characteristics of all subgroups that are relevant to the sponsor's requested reimbursement criteria: This includes: • Data for the population covered by the marketing authorization, if the trial population is broader than that covered by the marketing authorization. • The subgroup for whom the sponsor is positioning the technology if this population is narrower than that covered by the full indication approved or under review by Health Canada.	For the subgroups, a description of any imbalances between treatment arms or differences between the subgroups and whole trial population should be provided.
Primary outcomes (including for that are relevant to the sponsor's requested reimbursement criteria, if relevant) at the data cut included in the economic model.	Primary outcomes at the data cut which inform the regulatory submission should be reported because they are typically published within marketing authorization documentation (e.g., Product Monograph; Summary Basis for Decision; Regulatory Decision Summary).
Relative treatment effect and measure of precision such as 95% confidence interval.	If data from a later data cut than what informed the marketing authorization are used in the economic model and is marked as confidential, then the unredacted data

Standard reporting requirements	Minimum reporting requirements
	cut informing the marketing authorization should also be presented alongside the later data cut. Commentary should be provided on similarities or differences between the point estimates and confidence intervals from publicly available versus confidential data cuts. For subgroup data that will not be reported within marketing authorization documentation, an accompanying description of the direction of treatment effect and how the point estimate and measure of precision compare with the data for the whole population should be provided alongside the confidential information.
Kaplan–Meier data (including extrapolations), if relevant.	If Kaplan–Meier data from a later data cut than what informed the marketing authorization are used in the model and is marked as confidential, then the unredacted data cut informing the marketing authorization should also be presented alongside the later data cut. For overall survival extrapolation, the proportions of people alive at a range of time intervals over the time horizon should be provided to enable discussion of plausibility of this modelled outcome.
Secondary outcomes at the data cut that inform the modelling.	Follow the principles for the primary outcomes.
Adverse events including death.	The equivalent data to that reported in marketing authorization documentation is expected.
Indirect treatment comparison: • an overview of the methodological approach, including any matching of data or adjustments • number of patients included in studies • patient characteristics from included studies • commentary on potential heterogeneity or sources of bias	All methodology and critical appraisal should be reported. If there is a demonstrated reason why numerical outcomes are confidential then an accompanying statement of direction of treatment effect and commentary on the measure of precision should be provided. For example, the width of the credible intervals and if the credible intervals cross parity.

Standard reporting requirements	Minimum reporting requirements
• outcomes (for example, comparative efficacy) with measure of precision such as 95% credible interval, if relevant.	For adjusted outcomes, an accompanying description of how these outcomes differ from unadjusted outcomes should be provided.
Utility values (by health state, intervention utility increments or decrements, and disutility for adverse events) which are used in the model.	Quality of life data collected in the trial may be redactable.

B. Handling Confidential Information

1. Responsibilities of CDA-AMC

CDA-AMC will use reasonable care to prevent the unauthorized use, disclosure, publication, or dissemination of information received by CDA-AMC as part of the reimbursement review processes that has been designated confidential.

CDA-AMC will not disclose confidential information in and related to an application to any third party except as permitted by the confidentiality guidelines, or as required by law or by order of a legally qualified court or tribunal.

CDA-AMC will use confidential information solely for the purpose of carrying out its responsibilities with respect to the reimbursement review processes.

2. Responsibilities of Sponsors

Information identified as confidential information within an application is expected to be kept to a minimum. It is not acceptable to mark an entire section as confidential. Sponsors should make sure that such information has not already been disclosed in documents posted by other HTA agencies and/or regulatory authorities.

It is the responsibility of the sponsor to clearly identify (using highlighting) any information that it considers to be confidential, and to list the confidential information and clearly state the reason(s) for its confidentiality in a summary table provided by CDA-AMC.

Care should be taken when submitting information relating to individuals. Personal identifiers and sensitive information will be removed.

3. Release of Sponsor's Information

CDA-AMC may release any sponsor-supplied information received through the reimbursement review processes, including confidential information, to the following authorized recipients:

- CDA-AMC staff and review team members (including contractors and clinical experts)

- CDA-AMC expert committee members
- federal, provincial, and territorial government representatives (including their agencies and departments)
- pCPA office representative(s)
- CAPCA representative(s)
- Canadian Blood Services representative(s)
- members and observers of CDA-AMC's advisory committees and their associated working groups.

For drugs selected for joint engagement with clinical specialists by CDA-AMC and INESSS, CDA-AMC may release any sponsor-supplied information received through the reimbursement review processes, including confidential information, to INESSS expert committee members who are participating in meetings with the panel of clinical experts.

While CDA-AMC is an independent not-for-profit organization and is therefore not subject to access to information legislation, some of the authorized recipients listed previously have their own confidentiality procedures and are subject to freedom of information and access to information legislation over which CDA-AMC has no control.

CDA-AMC does not accept confidential submitted prices for applications filed for review through the reimbursement review processes. The submitted price is disclosed in all applicable CDA-AMC reports, as well as the recommendation documents posted on the CDA-AMC website. The outputs of economic models (e.g., incremental cost-effectiveness ratios) are not considered confidential and will not be redacted. Please refer to Table 39 which provides sponsors with guidance regarding what information that has been included in an application will and will not be considered redactable by CDA-AMC.

CDA-AMC staff members are required, as a condition of employment, to comply with CDA-AMC's confidentiality requirements, code of conduct, and conflict-of-interest policy. All the previously described authorized recipients (except for staff of federal, provincial, and territorial government representatives, including their agencies and departments; CAPCA; and pCPA) are required to sign a confidentiality agreement requiring them to comply with these confidentiality guidelines.

4. Documents Shared with Authorized Recipients

The documents that CDA-AMC may share with authorized recipients include, but are not limited to:

- advance notification and presubmission meeting materials provided by the sponsor
- the sponsor's submission, resubmission, or reassessment information
- information provided by a sponsor for a drug plan submission or a request for advice
- redacted and unredacted CDA-AMC review report
- the sponsor's comments about CDA-AMC's review report

- CDA-AMC's responses to the sponsor's comments about draft review report
- the redacted and unredacted draft recommendation
- the redacted and unredacted final recommendation
- correspondence between CDA-AMC and the sponsor regarding the drug under review
- committee briefing materials.

CDA-AMC provides the following documents to the sponsor (of which the sponsor must keep confidential until it is published on the CDA-AMC website):

- draft CDA-AMC review report
- CDA-AMC's responses to the sponsor's comments about draft review report
- the draft recommendation (until posted on the CDA-AMC website)
- the final recommendation (until posted on the CDA-AMC website).

The documents that CDA-AMC may post on its website include:

- a tracking document indicating the status of the review, including for a submission filed on a pre-NOC basis
- CDA-AMC review report (with confidential information redacted, if specified)
- a draft recommendation (with confidential information redacted, if specified)
- a final recommendation (with confidential information redacted, if specified).

5. Referring to Confidential Information in Public CDA-AMC Documents

CDA-AMC may use confidential information supplied by the sponsor in the preparation of the review report and recommendations. Before these documents are posted in the public domain, the sponsor will be asked to identify any confidential information for redaction in accordance with the confidentiality guidelines and the applicable sections of the Procedures for Reimbursement Reviews.

The following principles and provisions will apply to any confidential information that the sponsor has identified, and requests redacted from the review report, draft recommendation, or final recommendation:

- CDA-AMC will redact the confidential information using redaction software and will indicate that the sponsor requested that the confidential information be redacted, pursuant to the confidentiality guidelines.
- CDA-AMC may provide a general description of the type of information that was redacted and the reason(s), as provided by the sponsor.
- For greater clarity, information that does not meet the definition of confidential information as set out in section A of the confidentiality guidelines will not be redacted.

- When disagreement is expressed by the sponsor regarding redactions made in the review report and/or final recommendation, CDA-AMC may require additional time to resolve the disagreement in consultation with the sponsor. This additional time could delay posting of these documents; however, any such delays will not affect the timelines for issuing the final recommendation to the authorized recipients.
- If the sponsor fails to respond to the request to identify confidential information for redaction by the deadlines, CDA-AMC may proceed with posting the review report, draft recommendation, and/or final recommendation in accordance with the Procedures for Reimbursement Reviews.

C. Archiving of Documents Containing Confidential Information

CDA-AMC may retain copies of all documents associated with the review of a drug for as long as there may be a need to consult them. CDA-AMC will determine at its sole discretion if there is a need to consult this information. CDA-AMC staff undertake regular reviews of archived material. Any material that CDA-AMC determines to be no longer required will be disposed of. Any extra copies of documents at the completion of the review will be destroyed.

Appendix 2: Procedural Review

A. Purpose

The purpose of this section is to define the steps CDA-AMC will take to determine whether the established process outlined in the Procedures for Reimbursement Reviews was followed in the development of the final recommendation issued by a CDA-AMC expert committee for a pharmaceutical review. This section provides guidance for those who wish to make a request for a procedural review or who are considering doing so. A party that participated in the process relating to the final recommendation at issue may make a request for a procedural review; refer to paragraph C1 for further information on eligibility requirements.

If a request for procedural review is filed and accepted, CDA-AMC will publish a notice on its website indicating a procedural review is underway and notify the drug programs and the pCPA.

B. About Procedural Reviews

The ground for a procedural review relates only to whether the process was followed and not to the content or scientific issue that may or may not be included in the final recommendation (i.e., did CDA-AMC fail to act in accordance with its procedures in conducting the review and issuing the final recommendation). Such examples may include omitting input from eligible groups, deviating from the published steps without providing notice, failing to manage expert committee conflict of interest declaration in accordance with the CDA-AMC conflict of interest policy, or the expert committee exceeds the scope of its mandate.

A procedural review is not an opportunity to reopen issues that the CDA-AMC expert committee has decided on or to circumvent existing feedback mechanisms (e.g., request for reconsideration). This procedure also does not cover fairness in the colloquial sense; for instance, that it is “unfair” that a recommendation is issued to not reimburse a treatment. Unsubstantiated allegations of general unfairness, for example the alleged inability to understand a conclusion or the applicant simply disagrees with the views or conclusions in the final recommendation, will not be accepted as a valid ground for a procedural review.

This procedure is not intended to address concerns related to the methodology used in the development of a CDA-AMC process or in the interpretation and use of data during the review. For example, it would not be unfair if the expert committee considered the relevant dataset and reached a view with which the applicant did not agree.

In addition, disagreement with CDA-AMC’s approach to managing confidential information that was provided in the filed application dossier, including use or non-use in the review process, does not constitute grounds for a procedural review, provided processes were followed as outlined in the confidentiality guidelines (Appendix 1).

Requests for corrections of minor factual or typographical errors will not be grounds for a procedural review and will be addressed separately; CDA-AMC may issue an erratum in these instances.

If the issues identified are not resolved at the case conference stage, the adjudication of a procedural review request will be conducted by a procedural review panel ("panel") that will comprise individuals independent of the program directly responsible for the development of the final recommendation; refer to paragraph C6 for the composition of the panel. The panel will not re-adjudicate matters on which it has already provided a ruling. For clarity, matters that have been adjudicated by the panel are identified in the procedural review request form.

To promote transparency, processes for the development of the main types of CDA-AMC recommendations issued by a CDA-AMC expert committee are published on the CDA-AMC website. Parties are strongly encouraged to discuss their concerns about perceived deviations from the procedure with the CDA-AMC Pharmaceutical Reviews Directorate prior to filing a request for a procedural review by contacting CDA-AMC.

C. Procedure

1. Eligible Parties – Who Can File?

The following parties are eligible to submit a formal request to CDA-AMC for a procedural review:

- a sponsor that filed the submission or resubmission for the review in question (applies to reimbursement reviews)
- a company whose review was assessed as part of a therapeutic category or a class review in question (applies to therapeutic reviews)
- a patient group that provided input in response to a call for patient input for the review in question
- a clinician group that provided input in response to a call for clinician input for the review in question
- Formulary Working Group or Provincial Advisory Group members that engaged in the drug review reimbursement process.

Multiple parties, if eligible, may submit a request for a procedural review of a final recommendation issued by a CDA-AMC expert committee for a specific review but each of these parties may submit only 1 request per final recommendation review at issue within the 20-business day period. In cases where a request may be made by more than 1 eligible party and they are accepted for the same final recommendation review at issue, CDA-AMC will conduct the requests jointly for the purpose of the procedural review proceeding.

2. Requests for Formal Procedural Reviews – How to File?

A formal request to CDA-AMC may be made for a procedural review related to a final recommendation issued by a CDA-AMC expert committee for a specific review. A procedural review cannot be lodged against other documents produced during the process (for example, the draft recommendation or draft report).

Formal request for a procedural review must be made in writing using the designated procedural review request form and must be received within 20 business days of the final recommendation in question being posted on the CDA-AMC website.

The completed procedural review request form must include the full name of the party making the request, the contact information of the party filing the prescribed request form, the name of the CDA-AMC final recommendation in question, the involvement of the party with the final recommendation in question, and the details of the alleged deviation from procedure, including all supporting documents.

It is important that the prescribed request form is submitted correctly, is presented clearly, and contains the necessary information. If the request received is not appropriate (for example, the request does not have sufficient supporting information or the relevance of the issue is unclear), there is a possibility that the procedural review will be deemed “not valid” because it does not meet the ground for a procedural review. No extensions will be granted to the 20-business day period and all supporting documentation must be submitted within this period. Intent to submit supporting documentation after the 20-business day period will not be considered sufficient for initiation of the procedural review process.

Formal request using the designated Procedural Review Request form must be submitted to Requests@CDA-AMC.ca.

3. Receipt of Request(s) for Procedural Reviews

Upon receipt of the Procedural Review Request form, CDA-AMC will acknowledge receipt of the request.

4. Screening the Procedural Review Request Form

Upon receipt of the prescribed request form, CDA-AMC will screen and assess the request for the following requirements:

- applicant eligibility (i.e., the applicant is an eligible party as described in paragraph C1),
- completeness of the form and supporting document(s) is provided within the prescribed 20 business days, and
- the ground for a procedural review is met in accordance with the definition as set out in paragraph B.

If these conditions are met, CDA-AMC will notify the applicant in writing if the request has been accepted within 15 business days from the date of receipt of the prescribed request form by CDA-AMC.

Where a request for a procedural review has been made by someone other than the company that made the original submission or resubmission for the review in question (if applicable), CDA-AMC will notify the company and the participating drug programs if the procedural review has been accepted.

5. Case Conference

If a request for procedural review is accepted, the applicant(s) will be given an opportunity to conference with CDA-AMC. The purpose of the conference will be to narrow down or resolve the issue(s) in the procedural review request, including identifying those on which the panel has previously ruled, and identifying the steps required to rectify the situation. If the parties do not settle the issue and come to a mutual agreement within 5 business days, CDA-AMC will convene a panel to review the remaining issue(s) in dispute and the procedural review process steps and timelines will apply.

If a request is accepted, a notice indicating that a procedural review is in progress will be co-located with the file in question on the CDA-AMC website. Efforts will be made to complete this step within 7 business days from the date that the request is accepted.

The applicant(s) may bring up to 4 representatives knowledgeable about the issue(s) to the meeting. Legal representation is not permitted at this meeting.

6. Procedural Review Panel and Proceeding

The mandate and responsibilities of the panel are set out in a Charter. The panel will have responsibility for adjudicating procedural reviews that are not resolved at case conference and will only address such issues as remain unresolved between the parties. The panel will not re-adjudicate matters on which it has already provided a ruling, as identified in the procedural review request form.

A panel will comprise the following members selected by CDA-AMC:

- Past expert committee member
- Patient member
- A representative independent from CDA-AMC who is knowledgeable of the Canadian drug approval process.

The panel will aim to invite the applicant(s) to make a brief presentation within 30 business days of the conference date deadline, if an agreement cannot be reached during the conference period, to uncover as much information as possible about the alleged breach of process.

A maximum of 90 minutes will be allocated to present the issues that remain unresolved between the parties and to respond to questions from the panel. Where there are multiple eligible applicants, the maximum allowable time will not exceed 120 minutes and will be divided equally among the applicants in the joint proceeding meeting. Each requesting organization may bring up to 4 representatives knowledgeable about the issue at hand to the meeting. No legal representation is permitted at the meeting.

The meeting will be conducted via web/teleconference and will not be open to the public. The meeting will be recorded for internal use purposes. The panel may request additional information from the applicant and may also engage in additional internal fact-finding activities (e.g., interviews with the relevant director, other staff members, or other parties), as needed.

7. Making Decisions on Procedural Reviews and Targeted Timelines

The panel has sole and absolute discretion for determining whether the established process was or was not followed. Findings will be made based on the consensus of the panel members. Should a consensus not be reached, a decision will be made by a majority vote of the panel members. Decisions of the panel are final, and there is no possibility of making further procedural review requests against the decision of the panel.

The duration of the procedural review may vary, depending on the complexity and nature of the request. While efforts will be made to issue a decision in the shortest possible time, it may take up to a maximum of 60 business days to issue a decision from the date of receipt of the request for a formal procedural review.

A maximum of 1 procedural review per final recommendation will be undertaken (i.e., no additional procedural review requests may be filed against the same recommendation at issue).

8. Outcomes of Decision on Procedural Reviews

The panel may issue the following decision:

- No change to the existing specific review at issue and the CDA-AMC final recommendation will be upheld; or
- Steps in the review process for the specific review at issue must be revisited and/or the review must be redeliberated by the expert committee at the next available meeting. A re-deliberation may result in the expert committee's final recommendation being upheld or being revised.
    - If the original final recommendation is upheld following the re-deliberation, the original final recommendation will remain unchanged on the CDA-AMC website, and a note will be added to indicate that the procedural review was completed and that no changes were made to the original recommendation.
    - If the final recommendation is changed following the re-deliberation, the revised final recommendation will supersede the previous recommendation and will be publicly posted.

No further procedural review request will be permitted against the final recommendation at issue.

9. Communicating Decisions on Procedural Reviews and Posting on CDA-AMC Website

The applicant(s) will be informed of the decision of the panel. In cases where the panel finds that a deviation from process has occurred, CDA-AMC will identify the steps required to rectify the situation and will inform the applicant(s) of the decision and next steps, if applicable. In cases where the panel finds

that a deviation from process has occurred, the final recommendation at issue will be removed from the website and replaced with a notice indicating that additional work is underway and new targeted timelines due to the findings of the procedural review, until the matter can be appropriately remedied.

High-level details about the submitted procedural review request, including the name of the applicant(s), and the decision and reason for the decision, will be publicly posted on the CDA-AMC website.

Appendix 3: List of Templates

These templates are to be used whenever applicable (also available on CDA-AMC website).

Templates for Presubmission Phase

Advance notification form
Eligibility inquiry form
Evidence presentation meeting briefing paper template
Pharmaceutical submission SharePoint access request form
Pipeline meeting briefing paper template
Presubmission meeting briefing paper template
Presubmission meeting request form
Proposed place in therapy template

Templates for Requirements

Application overview template
Checklist for economic requirements
Declaration letter template
Executive summary template
Implementation plan for a cell or gene therapy
Letter for sending finalized indication template
Regulatory and HTA status template
Reimbursement status of comparators template
Sponsor summary of clinical evidence template
Table of studies template
Tailored review submission template

Templates for Input

Clinician group input template
Drug program input template
Industry input template (non-sponsored reimbursement reviews)
Input on implementation advice request
Input on scope of a provisional funding algorithm
Patient group input template

Templates for Feedback on Reports or Recommendations

Feedback on a draft provisional funding algorithm
Feedback on draft implementation advice
Feedback on draft recommendation
Reconsideration request template
Sponsor comments on draft reports template

Other Templates

Identification of confidential information template
Procedural review request template

Appendix 4: Checklists for Preparing Applications

Table 41: Clinical and Administrative Requirements: Standard or Complex Submission

Requirement	Specific items and criteria	Included
General information		
Application overview	Completed application overview template	—
Executive summary	Completed executive summary template for a submission (maximum 5 pages)	—
	Document is referenced	—
Product monograph	**Submission filed on a pre-NOC basis:** A copy of the most recent draft product monograph provided at the time of submission. After the NOC or NOC/c is issued: the sponsor must provide the draft product monograph with tracked changes and a clean and dated version of Health Canada–approved product monograph	—
	Submission filed on a post-NOC basis: The most current version of the Health Canada–approved product monograph	—
Declaration letter	Completed declaration letter template	—
Regulatory and HTA Status	Template with status at selected regulatory and HTA agencies as a Microsoft Word document. **Note:** Must be updated when filing comments on draft report.	—
Request for deviation	Request for deviation response letter or statement that a deviation was not requested	—
Sponsor Clinical Evidence Template		
Submission template	Complete sponsor summary of clinical evidence template	—
RIS file with references	RIS file with the references that have been cited in the sponsor summary of clinical evidence template	—
Health Canada documentation		
Letter of Undertaking	Letter of Undertaking (only if NOC/c granted)	—
Clarimails/Clarifaxes	**Submissions filed on a pre-NOC basis:** Summary table of clinical Clarimails/Clarifaxes up to time of filing. Updates must be provided on an ongoing basis until issuance of NOC or NOC/c: Revised Clarimail/Clarifax summary table(s)	—
	Submission filed on a post-NOC basis: Summary table of any clinical Clarimails/Clarifaxes up to issuance of NOC or NOC/c	—
Efficacy, effectiveness, and safety Information		
Common technical document	Section 2.5	—
	Section 2.7.3	—

Requirement	Specific items and criteria	Included
	Section 2.7.4	—
	Section 5.2	—
	Or a statement indicating which section(s) were not required by Health Canada	—
Clinical studies and errata	Reference list of key clinical studies (published and unpublished) and any errata	—
	Copies of studies addressing key clinical issues Copies of any errata (or a document stating that none found)	—
Clinical study reports	Clinical study reports for pivotal studies and other studies that address key clinical issues	—
Table of studies	Completed table of studies template (Microsoft Word or PDF document)	—
Validity of outcome measures	Reference list (or statement that none are available)	—
	Copies of validity of outcome measure references available	—
Indirect comparison	Copies of any indirect comparisons used in pharmacoeconomic evaluation	—
	Technical report	—
Reimbursement status of comparators		
Reimbursement status of comparators	A completed template summarizing the reimbursement status of all appropriate comparators as a Microsoft Word document	—
Pricing and distribution information		
Price and distribution method	Submitted unit pricing to four decimal places	—
	Method of distribution	—
Implementation plan	Completed implementation plan template (only for cell and gene therapies)	—
Provisional algorithm for oncology drugs		
Provisional algorithm (only for oncology drugs)	Place in therapy template	—
	A reference list (or statement that none are available)	—
	Copies of studies that address sequencing of therapies	—
	Copy of the search strategy for sequencing of therapies	—
Companion diagnostic (if applicable)		
Companion diagnostics	Reference list	—
	Copies of articles that highlight the clinical utility of the companion diagnostic(s)	—
	Disclosable price for the companion diagnostic(s)	—

Requirement	Specific items and criteria	Included
Additional letter for submissions filed on Pre-NOC basis		
Letter for sending finalized indication	**After NOC or NOC/c is issued:** A signed letter indicating whether any wording changes to the Health Canada–approved final product monograph result in revisions to the clinical or pharmacoeconomic information filed on a pre-NOC basis (used the provided letter template)	—

Table 42: Clinical and Administrative Requirements: Submission for a Tailored Review

Requirement	Specific items and criteria	Included
General information		
Application overview	Completed application overview template	—
Executive summary	Completed executive summary template for a submission (maximum 5 pages)	—
	Document is referenced	—
Product monograph	**Submission filed on a pre-NOC basis:** A copy of the most recent draft product monograph provided at the time of submission. After the NOC or NOC/c is issued: the sponsor must provide the draft product monograph with tracked changes and a clean and dated version of Health Canada–approved product monograph	—
	Submission filed on a post-NOC basis: The most current version of the Health Canada–approved product monograph	—
Declaration letter	Completed declaration letter template	—
Regulatory and HTA Status	Template with status at selected regulatory and HTA agencies as a Microsoft Word document. Note: Must be updated when filing comments on draft report.	—
Sponsor Clinical and Economic Summary Template		
Tailored review template	Completed tailored review template (PACES or Product Variation)	—
RIS file with references	RIS file with the references that have been cited in the tailored review template	—
Health Canada documentation		
Letter of undertaking (if applicable)	Letter of Undertaking (only if NOC/c granted)	—
Clarimails and Clarifaxes	**Submissions filed on a pre-NOC basis:** Summary table of clinical Clarimails/Clarifaxes up to time of filing. Updates must be provided on an ongoing basis until issuance of	—

Requirement	Specific items and criteria	Included
	NOC or NOC/c: Revised Clarimail/Clarifax summary table(s)	
	Submission filed on a post-NOC basis: Summary table of any clinical Clarimails/Clarifaxes up to issuance of NOC or NOC/c	—
Bioequivalence, efficacy, and safety evidence		
Common technical document	Section 2.5	—
	Section 2.7.3	—
	Section 2.7.4	—
	Section 5.2	—
	Or a statement indicating which section(s) were not required by Health Canada	—
Clinical studies and errata	Reference list	—
	Additional source documentation for data reported in the tailored review template	—
Clinical study reports	Complete clinical study reports for all pivotal studies as well as other studies that address key clinical issues	—
Table of studies	Completed table of studies template (Microsoft Word or PDF document)	—
Reimbursement status of comparators		
Reimbursement status of comparators	A completed template summarizing the reimbursement status of all appropriate comparators as a Microsoft Word document	—
Pricing and distribution information		
Price and distribution Method	Submitted unit pricing to four decimal places	—
	Method of distribution	—
Additional letter for submissions filed on Pre-NOC basis		
Letter for sending finalized indication	After NOC or NOC/c is issued: A signed letter indicating whether any wording changes to the Health Canada–approved final product monograph result in revisions to the clinical or pharmacoeconomic information filed on a pre-NOC basis (use the provided letter template)	—

Table 43: Clinical and Administrative Requirements: Resubmission

Section	Specific Items and Criteria	Included
General information		
Application overview	Completed application overview template	—
Executive summary	Completed executive summary template for a resubmission (maximum 5 pages)	—
	Document referenced with all supporting references	—
Product monograph	The most current version of the Health Canada–approved product monograph	—
Declaration letter	Completed declaration letter template	—
Regulatory and HTA Status	Template with status at selected regulatory and HTA agencies as a Microsoft Word document. Note: Must be updated when filing comments on draft report.	—
Request for deviation	Request for deviation response letter or statement that a deviation was not requested	—
Sponsor Clinical Evidence Template		
Submission template	Complete sponsor summary of clinical evidence template	—
RIS file with references	RIS file with the references that have been cited in the sponsor summary of clinical evidence template	—
Efficacy, effectiveness, and safety information		
Common technical document	Section 2.5	—
	Section 2.7.3	—
	Section 2.7.4	—
	Section 5.2	—
	Or a statement indicating any section(s) not required for Health Canada submission	—
Clinical studies and errata that were included in the initial submission	Reference list of key clinical studies (published and unpublished) and any errata provided in the initial submission and any previous resubmissions	—
	Copies of studies addressing key clinical issues	—
Clinical study reports	Complete clinical study reports for all pivotal studies as well as other studies that address key clinical issues	—
Validity of outcome measures	Reference list for validity of outcome measures (or document stating none found)	—
	Copies of validity of outcome measure references available	—

Section	Specific Items and Criteria	Included
Table of studies	An updated tabulated list of all published and unpublished clinical studies using the provided table of studies template (Microsoft Word or PDF document)	—
Indirect comparison	Copies of any indirect comparisons used in the pharmacoeconomic evaluation	—
	Indirect comparison technical report	—
Reimbursement status of comparators		
Reimbursement status of comparators	A completed template summarizing the reimbursement status of all appropriate comparators as a Microsoft Word document	—
Pricing and distribution information		
Price and distribution method	Submitted unit pricing to 4 decimal places	—
	Method of distribution	—
Provisional algorithm for oncology drugs		
Provisional algorithm (only for oncology drugs)	Place in therapy template	—
	A reference list (or statement that none are available)	—
	Copies of studies that address sequencing of therapies	—
	Copy of the search strategy for sequencing of therapies	—
Companion diagnostic(s)		
Companion diagnostics	Reference list and copies of articles that highlight the clinical utility of the companion diagnostic(s)	—
	Disclosable price for the companion diagnostic(s)	—

Table 44: Clinical and Administrative Requirements: Reassessment

Section	Specific items and criteria	Included
General information		
Application overview	Completed application overview template	—
Executive summary	Completed executive summary template for a reassessment (maximum 5 pages)	—
	Document referenced with all supporting references	—
Product monograph	The most current version of the Health Canada–approved product monograph	—
Declaration letter	Completed declaration letter template	—
Regulatory and HTA Status	Template with status at selected regulatory and HTA agencies as a Microsoft Word document. Note: Must be updated when filing comments on draft report.	—

Section	Specific items and criteria	Included
Request for deviation	Request for deviation response letter or statement that a deviation was not requested	—
Sponsor Clinical Summary Template		
Submission template	Complete sponsor summary of clinical evidence template	—
RIS file with references	RIS file with the references that have been cited in the sponsor summary of clinical evidence template	—
Efficacy, effectiveness, and safety Information		
New clinical studies	Reference lists of all new clinical studies and errata (or a document stating none is available) included in the reassessment	—
	Copies of all new clinical information and errata	—
Clinical study reports	Complete clinical study reports for all new studies included in the reassessment	—
Validity of outcome measures	Reference list for validity of outcome measures (or document stating none found)	—
	Copies of validity of outcome measure references available	—
Table of studies	An updated tabulated list of all published and unpublished clinical studies using the provided table of studies template (Microsoft Word or PDF document)	—
Indirect comparison	Copies of any indirect comparisons used in the pharmacoeconomic evaluation	—
	Indirect comparison technical report	—
Reimbursement status of comparators		
Reimbursement status of comparators	A completed template summarizing the reimbursement status of all appropriate comparators as a Microsoft Word document	—
Pricing and distribution information		
Price and distribution method	Submitted unit pricing to 4 decimal places	—
	Method of distribution	—
Provisional algorithm for oncology drugs		
Provisional algorithm (only for oncology drugs)	Place in therapy template	—
	A reference list (or statement that none are available)	—
	Copies of studies that address sequencing of therapies	—
	Copy of the search strategy for sequencing of therapies	—
Companion diagnostic(s)		
Companion diagnostics	Reference list and copies of articles that highlight the clinical utility of the companion diagnostic(s)	—

Section	Specific items and criteria	Included
	Disclosable price for the companion diagnostic(s)	—

Table 45: Pharmacoeconomic Requirements

Requirement	Specific items and criteria	Included
Checklist of economic requirements		
Checklist	Completed checklist of economic requirements	—
Cost-Utility Analysis		
Pharmacoeconomic evaluation: technical report	**Submission or Resubmission:** • Pharmacoeconomic evaluation reflects the full population identified in the Health Canada indication(s) to be reviewed • Scenario analysis of the population identified in the reimbursement request (if different from the population in the full indication) • Other relevant scenario analyses presented	—
	Reassessments: • Pharmacoeconomic evaluation reflects the scope of the reassessment: • Population covered under the proposed revised reimbursement criteria • Population covered under the current reimbursement criteria • Relevant scenario analyses	—
	All relevant comparators have been included	—
	Rationale provided if potentially relevant comparators excluded	—
	Base case reflects the public health care payer perspective	—
	1.5% discount rate on costs and QALYs	—
	Treatment effect measures are based on composite end points	—
	Submitted price per smallest dispensable unit used	—
	All submitted forms and strengths included	—
	Base case is presented probabilistically	—
	Base-case results are presented deterministically	—
	All ICERs reported sequentially if more than one comparator is presented	—
	Results are presented in disaggregated format	—
	QALYs, life-years and costs are reported	—
	If relevant, companion diagnostic test information incorporated	—
	Alignment between the pharmacoeconomic evaluation technical report and the economic model	—

Requirement	Specific items and criteria	Included
Checklist of economic requirements		
Checklist	Completed checklist of economic requirements	—
Economic model	Model is programmed in Excel	—
	Model is fully unlocked and executable, and all code is provided	—
	Model functions in a stand-alone environment and does not require access to a web-based platform	—
	Probabilistic analyses run without error	—
	CDA-AMC can easily vary any individual input and view calculation	—
	Results of the probabilistic analysis are stable (congruence test provided)	—
	If used, seeding must be easily disabled or modifiable	—
	The model runs treatments simultaneously and results of all comparators are presented	—
	If relevant, flexible to assess all parametric distributions tested by the sponsor; present graphically the Kaplan-Meier and parametric curves to allow visual inspection of fit concurrently, within one graph	—
	Markov or event-time trace is provided via formulas within the Excel worksheets	—
	Model run time is no more than 1 business day (8 hours)	—
	Does not require CDA-AMC to agree to terms and conditions or have a legal disclaimer	—
Cost-Minimization Analysis		
Pharmacoeconomic evaluation: technical report	Drug is a new treatment in an existing therapeutic class in which there are treatments already reimbursed	—
	Drug under review demonstrates similar clinical effects compared with the most appropriate comparator(s)	—
	Submission or Resubmission: • Pharmacoeconomic evaluation reflects the full population identified in the indication(s) to be reviewed • Scenario analysis of the population identified in the reimbursement request (if different from the population in the full indication) **Reassessments:** • Pharmacoeconomic evaluation reflects the scope of the reassessment: • Population covered under the proposed revised reimbursement criteria • Population covered under the current reimbursement criteria	—
	All relevant comparators have been included	—

Requirement	Specific items and criteria	Included
Checklist of economic requirements		
Checklist	Completed checklist of economic requirements	—
	Rationale provided if potentially relevant comparators excluded	—
	Base case reflects the public health care payer perspective	—
	1.5% discount rate on costs if time horizon greater than 1 year	—
	Submitted price per smallest dispensable unit used	—
	All submitted forms and strengths included	—
	All results are presented probabilistically unless rationale for absence of parameter uncertainty	—
	Results are presented in disaggregated format	—
	Alignment between the pharmacoeconomic evaluation technical report and the economic model	—
Cost calculations	Excel workbook provided	—
	Workbook is fully unlocked and all calculations provided	—
	Model functions in a stand-alone environment, does not require access to a web-based platform, and all code is provided.	—
	CDA-AMC can easily vary any individual input and trace inputs through the workbook	—
	If probabilistic, analyses run simultaneously for all comparators without error, and results are stable over multiple runs	—
	Model run time is no more than 1 business day (8 hours)	—
	Does not require CDA-AMC to agree to terms and conditions or have a legal disclaimer	—
Supporting documentation for the Pharmacoeconomic Evaluation		
Supporting documentation	Economic model user guide	—
	Unpublished studies or analyses used to inform the pharmacoeconomic evaluation, including technical report of the indirect comparison(s), utility studies, etc., provided within 1 folder. Reference numbering aligns with the pharmacoeconomic evaluation report.	—
	All other supporting documentation (i.e., references) used and/or cited in the pharmacoeconomic evaluation provided within one folder. Reference numbering aligns with the pharmacoeconomic evaluation report.	—
	Document summarizing key sources of information for the companion diagnostic test	—
	1 RIS file with references for both the pharmacoeconomic evaluation and budget impact analysis	—

Table 46: Budget Impact Analysis Requirements

Requirement	Specific items and criteria	Included
Budget impact analysis		
Budget impact analysis: technical report	Base case reflects pan-Canadian (national) drug program perspective (excluding Quebec)	—
	For PPRP reviews, an analysis from the Canadian Blood Services perspective is provided.	—
	For cell and gene therapies, products administered partially or solely in hospital, or infusion therapies, a scenario that considers the Canadian health system perspective has been provided	—
	Population(s) assessed in the base case and scenarios align with the economic evaluation	—
	Base-case analysis uses a 1-year baseline period and 3-year forecast period	—
	All relevant comparators included (aligns with the economic evaluation)	—
	Submitted price per smallest dispensable unit used	—
	All submitted forms and strengths are included	—
	Results presented deterministically	—
	Results presented for each specified jurisdiction before being aggregated to pan-Canadian results	—
	Report includes at minimum decision problem, methods, assumptions and results	—
	Alignment between the technical report and the model	—
Budget impact model	Model is programmed in Excel	—
	Model is fully unlocked and executable, and all code is provided.	—
	Model functions in a stand-alone environment and does not require access to a web-based platform	—
	CDA-AMC must be able to vary individual parameters, view the calculations, and run the model to generate results	—
	Model is flexible and allows assessment of each specified individual drug program	—
	Input values specific to the individual drug program	—
	Breakdown of costs by perspective reported within the submitted model	—
	Does not require CDA-AMC to agree to terms and conditions or have a legal disclaimer	—
Supporting documentation for the Budget Impact Analysis		
Supporting documentation	Unpublished studies or analyses used to inform the BIA provided within one folder. Reference numbering aligns with the BIA report.	—

Requirement	Specific items and criteria	Included
	All other supporting documentation (i.e., references) used and/or cited in the BIA provided within one folder. Reference numbering aligns with the BIA report.	—
	References for the budget impact analysis must be included in the RIS file required for the pharmacoeconomic evaluation	—

Appendix 5: File Structure and Naming Format

Instructions for Sponsors

Please carefully review the following file structure and naming conventions before assembling the application requirements. If you have any questions, please contact CDA-AMC with the complete details of your question(s).

Filing Requirements

All materials must be submitted using the Pharmaceutical Submissions SharePoint site. Sponsors should review the Pharmaceutical Submissions SharePoint Site – Setup Guide for full instructions on how to setup a project folder for their submission and gain access to the site. Sponsors must complete the steps outlined in the guide to request access to the site a **minimum of 10 business days** prior to their submission of any document (this is typically the Presubmission Meeting Request Form or the Advanced Notification Form [if not requesting a presubmission meeting]). In the event the sponsor has not requested or received access prior to their target date for providing advance notification of the pending application, please contact CDA-AMC immediately. CDA-AMC will work with the sponsor to ensure there is no delay.

Files should be submitted as zipped (.zip) files. If there are several .zip files, the number of files should be noted in the file name (e.g., 1of4). The root folder(s) should be clearly named with the brand or generic drug name. An email notification will be sent to the sponsor when the file has been submitted successfully.

The entire decoded file path, including the file name, cannot contain more than 400 characters. The limit applies to the combination of the folder path and file name after decoding. Documents must be provided in PDF or Microsoft Word format, unless otherwise indicated in the requirement descriptions. These files must be unlocked, searchable, and printable. Document users must be able to extract information or combine documents.

Documents must be organized and labelled according to the file structure and naming format provided in this appendix. If any extra supporting documents that do not have a designated folder are being submitted at the sponsor's discretion (e.g., clinical study reports), these should be appropriately named and filed in a logical location in the file structure.

Providing Additional Information During the Review

If CDA-AMC requests additional information during the review, sponsors must provide the requested information using the Pharmaceutical Submissions SharePoint site in the "4. Additional Information" folder. Files should be submitted as zipped (.zip) files. The documents within the .zip file must be provided in PDF or Microsoft Word format. These files must be unlocked, searchable, and printable. Document users must be able to extract information or combine documents.

Submission Requirements for a Standard Review

Folder title: Brand Name

Folder title: 1_Brand Name_General Information

- 1 - Application Overview
- 2 - Executive Summary
- 3 - Product Monograph
- 4 - Declaration letter
- 5 - Regulatory-HTA Status
- 6 - Request for Deviation

Folder title: 2_Brand Name_Sponsor Clinical Evidence

- 1 - Brand Name Clinical Evidence
- 2 - Brand Name References (Note: this must a RIS file)

Folder title: 3_Brand Name_Health Canada Documentation

- 1 - Table of Clarimails
- 2 - Letter of Undertaking (Note: only if applicable)

Folder title: 4_Brand Name_Clinical Information

Folder title: 4.1_Common Technical Document

- 1 - Section 2.5
- 2 - Section 2.7.3
- 3 - Section 2.7.4
- 4 - Section 5.2

Folder title: 4.2_Clinical Studies and Errata

- _List of Studies and Errata
- 1 - Trial Name_Author_Year
- 2 - Trial Name_Author_Year Erratum

Folder title: 4.3_Clinical Study Reports

- 1 - Trial Name

- 2 - Trial Name

Folder title: 4.4_Table of Studies

- Table of Studies

Folder title: 4.5_Validity of Outcomes

- _List of References
- 1 - Author_Year

Folder title: 4.6_Indirect Comparison

- Indirect Comparison
- Technical report

Folder title: 5_Brand Name_Comparator Status

- Comparator Reimbursement Status

Folder title: 6_Brand Name_Economic

- Pharmacoeconomic evaluation
- Economic model
- Checklist for economic requirements
- RIS file with economic references

Folder title: Supporting documentation

Folder title: Published

Folder title: Unpublished

Folder title: 7_Brand Name_BIA

Folder title: 7.1_BIA Report

- pan-Canadian BIA Report

Folder title: 7.2_BIA Model

- pan-Canadian BIA Model

Folder title: 7.3_BIA Supporting Documentation

Folder title: Published

Folder title: Unpublished

Folder title: 8_Brand Name_Pricing and Distribution

- Pricing and Distribution

Folder title: 9_Brand Name_Provisional Algorithm

- Brand Name_Place In Therapy
- Brand Name_List of References
- 1 - Author_Year

Folder title: 10_Brand Name_Companion Diagnostic

Folder title: 10.1_Clinical Utility

- _List of References
- 1 – Author_Year

Folder title: 10.2_Price

- Companion Diagnostic Price

Submission Requirements for a Complex Review

Folder title: Brand Name

Folder title: 1_Brand Name_General Information

- 1 - Application Overview
- 2 - Executive Summary
- 3 - Product Monograph
- 4 - Declaration letter
- 5 - Regulatory-HTA Status
- 6 - Request for Deviation

Folder title: 2_Brand Name_Sponsor Clinical Evidence

- 1 - Brand Name Clinical Evidence
- 2 - Brand Name References (Note: this must a RIS file)

Folder title: 3_Brand Name_Health Canada Documentation

- 1 - Table of Clarimails
- 2 - Letter of Undertaking (Note: only if applicable)

Folder title: 4_Brand Name_Clinical Information

Folder title: 4.1_Common Technical Document

- 1 - Section 2.5
- 2 - Section 2.7.3
- 3 - Section 2.7.4
- 4 - Section 5.2

Folder title: 4.2_Clinical Studies and Errata

- _List of Studies and Errata
- 1 - Trial Name_Author_Year
- 2 - Trial Name_Author_Year Erratum

Folder title: 4.3_Clinical Study Reports

- 1 - Trial Name
- 2 - Trial Name

Folder title: 4.4_Table of Studies

- Table of Studies

Folder title: 4.5_Validity of Outcomes

- _List of References
- 1 - Author_Year

Folder title: 4.6_Indirect Comparison

- Indirect Comparison
- Technical report

Folder title: 5_Brand Name_Comparator Status

- Comparator Reimbursement Status

Folder title: 6_Brand Name_Economic

- Pharmacoeconomic evaluation
- Economic model
- Checklist for economic requirements
- RIS file with economic references

Folder title: Supporting documentation

Folder title: Published

Folder title: Unpublished

Folder title: 7_Brand Name_BIA

Folder title: 7.1_BIA Report

- pan-Canadian BIA Report

Folder title: 7.2_BIA Model

- pan-Canadian BIA Model

Folder title: 7.3_BIA Supporting Documentation

Folder title: Published

Folder title: Unpublished

Folder title: 8_Brand Name_Pricing and Distribution

- Pricing and Distribution

Folder title: 9_Brand Name_Implementation Plan *(for cell and therapies only)*

- Implementation Plan

Folder title: 10_Brand Name_Provisional Algorithm *(for oncology drugs only)*

- Brand Name_Place In Therapy
- Brand Name_List of References
- 1 - Author_Year

Folder title: 11_Companion Diagnostic

Folder title: 11.1_Clinical Utility

- _List of References
- 1 - Author_Year

Folder title: 11.2_Price

- Companion Diagnostic Price

Submission Requirements for a Plasma Protein and Related Product Review

Folder title: Brand Name

Folder title: 1_Brand Name_General Information

- 1 - Application Overview
- 2 - Executive Summary
- 3 - Product Monograph
- 4 - Declaration letter
- 5 - Regulatory-HTA Status
- 6 - Request for Deviation

Folder title: 2_Brand Name_Sponsor Clinical Evidence

- 1 - Brand Name Clinical Evidence
- 2 - Brand Name References (Note: this must a RIS file)

Folder title: 3_Brand Name_Health Canada Documentation

- 1 - Table of Clarimails
- 2 - Letter of Undertaking (Note: only if applicable)

Folder title: 4_Brand Name_Clinical Information

Folder title: 4.1_Common Technical Document

- 1 - Section 2.5
- 2 - Section 2.7.3
- 3 - Section 2.7.4
- 4 - Section 5.2

Folder title: 4.2_Clinical Studies and Errata

- _List of Studies and Errata
- 1 - Trial Name_Author_Year
- 2 - Trial Name_Author_Year Erratum

Folder title: 4.3_Clinical Study Reports

- 1 - Trial Name

- 2 - Trial Name

Folder title: 4.4_Table of Studies

- Table of Studies

Folder title: 4.5_Validity of Outcomes

- _List of References
- 1 - Author_Year

Folder title: 4.6_Indirect Comparison

- Indirect Comparison
- Technical report

Folder title: 5_Brand Name_Comparator Status

- Comparator Reimbursement Status

Folder title: 6_Brand Name_Economic

- Pharmacoeconomic evaluation
- Economic model
- Checklist for economic requirements
- RIS file with economic references

Folder title: Supporting documentation

Folder title: Published

Folder title: Unpublished

Folder title: 8_Brand Name_BIA

Folder title: 8.1_BIA Report

- pan-Canadian BIA Report

Folder title: 8.2_BIA Model

- pan-Canadian BIA Model

Folder title: 8.3_BIA Supporting Documentation

Folder title: Published

Folder title: Unpublished

Folder title: 9_Brand Name_Pricing and Distribution

- Pricing and Distribution

Folder title: 10_Companion Diagnostic

Folder title: 10.1_Clinical Utility

- _List of References
- 1 - Author_Year

Folder title: 10.2_Price

- Companion Diagnostic Price

Submission Requirements for a Tailored Review

Folder title: Brand Name

Folder title: 1_Brand Name_General Information

- 1 - Application Overview
- 2 - Executive Summary
- 3 - Product Monograph
- 4 - Declaration Letter
- 5 - Regulatory-HTA Status

Folder title: 2_Brand Name_Health Canada Documentation

- 1 - Table of Clarimails
- 2 - Letter of Undertaking (Note: only if applicable)

Folder title: 3_Brand Name_Submission Template

- 1 - Tailored Review Submission Template

Folder title: 4_Brand Name_Clinical Information

Folder title: 4.1_Common Technical Document

- 1 - Section 2.5
- 2 - Section 2.7.3
- 3 - Section 2.7.4
- 4 - Section 5.2

Folder title: 4.2_Source Documentation

- _List of Documentation
- 1 - Name_Year
- 2 - Name_Year

Folder title: 4.3_Clinical Study Reports

- 1 - Trial Name
- 2 - Trial Name

Folder title: 4.4_Table of Studies

- Table of Studies

Folder title: 5_Brand Name_Comparator Status

- Comparator Reimbursement Status

Folder title: 6_Brand Name_Pricing and Distribution

- Pricing and Distribution

Folder title: 7_Brand Name_BIA

Folder title: 7.1_BIA Report

- pan-Canadian BIA Report

Folder title: 7.2_BIA Model

- pan-Canadian BIA Model

Folder title: 7.3_BIA Supporting Documentation

Folder title: Published

Folder title: Unpublished

Folder title: 8_Companion Diagnostic

Folder title: 8.1_Clinical Utility

- _List of References
- 1 - Author_Year

Folder title: 8.2_Price

- Companion Diagnostic Price

Resubmission Requirements

Folder title: Brand Name

Folder title: 1_Brand Name_General Information

- 1 - Application Overview
- 2 - Executive Summary
- 3 - Product Monograph
- 4 - Declaration letter
- 5 - Regulatory-HTA Status
- 6 - Request for Deviation

Folder title: 2_Brand Name_Sponsor Clinical Evidence

- 1 - Brand Name Clinical Evidence
- 2 - Brand Name References (Note: this must a RIS file)

Folder title: 3_Brand Name_Clinical Information

Folder title: 3.1_Common Technical Document

- 1 - Section 2.5
- 2 - Section 2.7.3
- 3 - Section 2.7.4
- 4 - Section 5.2

Folder title: 3.2_Clinical Studies and Errata

- _List of Studies and Errata
- 1 - Trial Name_Author_Year
- 2 - Trial Name_Author_Year Erratum

Folder title: 3.3_Clinical Study Reports

- 1 - Trial Name
- 2 - Trial Name

Folder title: 3.4_Validity of Outcomes

- List of References

- 1 - Author_Year

Folder title: 3.5_Updated Table of Studies

- Table of Studies

Folder title: 3.6_Indirect Comparison

- Indirect Comparison
- Technical report

Folder title: 4_Brand Name_Comparator Status

- Comparator Reimbursement Status

Folder title: 5_Brand Name_Economic

- Pharmacoeconomic evaluation
- Economic model
- Checklist for economic requirements
- RIS file with economic references

Folder title: Supporting documentation

Folder title: Published

Folder title: Unpublished

Folder title: 6_Brand Name_BIA

Folder title: 6.1_BIA Report

- pan-Canadian BIA Report

Folder title: 6.2_BIA Model

- pan-Canadian BIA Model

Folder title: 6.3_BIA Supporting Documentation

- **Folder title:** Published
- **Folder title:** Unpublished

Folder title: 7_Brand **Name_Pricing and Distribution**

- Pricing and Distribution

Folder title: 8_Brand Name_Provisional Algorithm

- Brand Name_Place In Therapy
- Brand Name_List of References
- 1 - Author_Year

Folder title: 9_Companion Diagnostic

Folder title: 9.1_Clinical Utility

- _List of References
- 1 - Author_Year

Folder title: 9.2_Price

- Companion Diagnostic Price

Standard Reassessment Requirements

Folder title: Brand Name

Folder title: 1_Brand Name_General Information

- 1 - Application Overview
- 2 - Executive Summary
- 3 - Product Monograph
- 4 - Declaration letter
- 5 - Regulatory-HTA Status
- 6 - Request for Deviation

Folder title: 2_Brand Name_Sponsor Clinical Evidence

- 1 - Brand Name Clinical Evidence
- 2 - Brand Name References (Note: this must a RIS file)

Folder title: 3_Brand Name_Clinical Information

Folder title: 3.1_Clinical Studies and Errata

- _List of Clinical Studies and Errata
- 1 - Trial Name_Author_Year

- 2 - Trial Name_Author_Year

Folder title: 3.2_Clinical Study Reports

- 1 - Trial Name
- 2 - Trial Name

Folder title: 3.3_Validity of Outcomes

- List of References
- 1 - Author_Year

Folder title: 3.4_Updated Table of Studies

- Table of Studies

Folder title: 3.5_Indirect Comparison

- Indirect Comparison
- Technical report

Folder title: 4_Brand Name_Comparator Status

- Comparator Reimbursement Status

Folder title: 5_Brand Name_Economic

- Pharmacoeconomic evaluation
- Economic model
- Checklist for economic requirements
- RIS file with economic references

Folder title: Supporting documentation

Folder title: Published

Folder title: Unpublished

Folder title: 6_Brand Name_BIA

Folder title: 6.1_BIA Report

- pan-Canadian BIA Report

Folder title: 6.2_BIA Model

- pan-Canadian BIA Model

Folder title: 6.3_BIA Supporting Documentation

Folder title: Published

Folder title: Unpublished

Folder title: 7_Brand Name_Pricing and Distribution

- Pricing and Distribution

Folder title: 8_Brand Name_Provisional Algorithm

- Brand Name_Place In Therapy
- Brand Name_List of References
- 1 - Author_Year

Folder title: 9_Companion Diagnostic

Folder title: 9.1_Clinical Utility

- _List of References
- 1 - Author_Year

Folder title: 9.2_Price

- Companion Diagnostic Price

Appendix 6: Key Definitions

The following are high-level definitions for key terms used in this document. Readers should consult the appropriate sections of the document for more detailed context as it relates to some terms.

Active substance: A therapeutic substance that has pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease (refer to new active substance).

Additional information: Additional information includes any information that is additional to the documents that are required for an application to be accepted for review. This information is requested from the sponsor to complete the review or to clarify information.

Application: Written documentation filed by a sponsor to have a drug reviewed through the reimbursement review process.

Appropriate comparator: Typically, a drug listed by one or more drug programs for the indication under review. However, the choice of appropriate comparator(s) in reviews is made on a case-by-case basis.

Biosimilar: A biosimilar is a biologic drug (i.e., a drug derived from living sources versus a chemically synthesized drug) that demonstrates a high degree of similarity to an already authorized biologic drug (i.e., a “reference product” that has been authorized in Canada, or in some circumstances can be an authorized non-Canadian biologic from a jurisdiction that has an established relationship with Health Canada).

Business day: Any day (other than a Saturday, Sunday, statutory holiday, or company holiday) on which the CDA-AMC office in Ottawa (Ontario, Canada) is open for business during regular business hours. Please refer to the Holiday Schedule.

Business hours: Any weekday (excluding statutory and company holidays) from 8:00 a.m. to 4:00 p.m. Eastern time.

Review team: A team assembled to undertake a reimbursement review. The review team may include CDA-AMC staff, contracted reviewers, and external experts with appropriate qualifications and expertise.

Cancelled review: The cessation of the review before all steps of the review process are completed.

Committee brief: A compilation of the materials regarding a drug under review, prepared by CDA-AMC staff for the members of the expert committee.

Companion diagnostic test: A medical device that provides information that is essential for the safe and effective use of corresponding drugs or biological products. They can identify patients who are likely to benefit or experience harms from particular therapeutic products or monitor clinical response to optimally guide treatment adjustments. Companion diagnostics detect specific biomarkers that predict more favourable responses to particular therapeutic products.

Date of acceptance for review: The date on which CDA-AMC has confirmed with the sponsor that the key requirements for initiating the review process have been met.

Date of filing: The date on which an application is received.

Date of initiation: The date on which the assigned CDA-AMC review team begins work on a review.

Drug: An active substance considered to be a drug under the Canadian Food and Drugs Act and Food and Drug Regulations that has been granted by Health Canada (or will be granted in the case of a submission filed on a pre-Notice of Compliance basis) a Notice of Compliance or Notice of Compliance with conditions and is approved for human use.

Drug programs: The federal, provincial, and territorial drug programs participating in the CDA-AMC Reimbursement Review processes.

Final recommendation: A document that provides guidance to the drug programs participating in the reimbursement review processes to make a reimbursement decision for the drug under review. Final recommendations are non-binding to the drug programs.

Formulary Working Group: A working group of the Pharmaceutical Advisory Committee. Formulary Working Group provides advice to CDA-AMC on pharmaceutical issues and helps with the effective jurisdictional sharing of pharmaceutical information.

Generic drugs: Copies of Canadian reference products (i.e., Health Canada–approved brand name drugs) that demonstrate bioequivalence on the basis of pharmaceutical equivalence (i.e., they contain identical amounts of the identical active medicinal ingredients as the reference product, in comparable dosage forms, but do not necessarily contain the same non-medicinal ingredients as the Canadian reference product, and the conditions of use fall with those of the Canadian reference product) and bioavailability characteristics, where applicable, with the Canadian reference product. Generic drugs are not typically reviewed through the reimbursement review processes.

New active substance: A therapeutic substance that has never been approved for marketing in Canada in any form. It may be:

- a chemical or biological substance not previously approved for sale in Canada as a drug
- an isomer, derivative, or salt of a chemical substance previously approved for sale as a drug in Canada but differing in properties regarding safety and efficacy.

New combination product: Consists of 2 or more drugs that have not been previously marketed in Canada in that combination. It may consist of either 2 or more new drugs, 2 or more previously marketed drugs, or a combination of new drug(s) and previously marketed drug(s).

New drug: A therapeutic substance that has never been approved for marketing in any form, regardless of when the Notice of Compliance or Notice of Compliance with conditions was issued. It may be: a chemical or biological substance not previously approved for sale in Canada as a drug; or an isomer,

derivative, or salt of a chemical substance previously approved for sale as a drug in Canada but differing in properties regarding safety and efficacy.

New indication: A disease condition for which the use of a particular drug has not previously been approved by Health Canada.

New information: New clinical information and/or new cost information that was not part of an originally filed application.

Notice of Compliance: Authorization issued by Health Canada to market a drug in Canada when regulatory requirements for the safety, efficacy, and quality are met.

Notice of Compliance with conditions: Authorization issued by Health Canada to market a drug under the Notice of Compliance with conditions policy. This indicates that the sponsor has agreed to undertake additional studies to confirm the clinical benefit of the product.

Patient group: An organized group of patients or caregivers in Canada.

Post-Notice of Compliance: The timing of filing a submission after Health Canada has granted a Notice of Compliance or Notice of Compliance with conditions for the indication(s) to be reviewed.

Pre-Notice of Compliance: The timing of filing a submission before Health Canada has granted a Notice of Compliance or Notice of Compliance with conditions for the indication(s) to be reviewed, and for which the anticipated date of Notice of Compliance or Notice of Compliance with conditions is within 180 calendar days of the submission being filed.

Provincial Advisory Group: A working group of the Pharmaceutical Advisory Committee. The Provincial Advisory Group provides advice to CDA-AMC on pharmaceutical issues and helps with the effective jurisdictional sharing of pharmaceutical information.

Queuing: A delay in the initiation of a review.

Reasons for recommendation: These represent the key considerations and rationale used by the expert committee in formulating the recommendation.

Request for reconsideration: A written request from a sponsor or the drug programs for a draft recommendation to be reconsidered by the expert committee.

Sponsor: A person, corporation, or entity eligible to file an application for a reimbursement review. The sponsor could be a manufacturer, a supplier, a corporation, or entity recruited by the manufacturer or the supplier.

Submitted price: The submitted price is the price per smallest dispensable unit that is submitted to CDA-AMC and that must not be exceeded for any of the drug programs following completion of the review. The submitted price will be disclosed in all applicable CDA-AMC reports.

Suspended review: The temporary cessation of a reimbursement review. This occurs if questions or issues arise outside of the regular review process or if the review team is unable to perform a thorough assessment of the application due to incomplete or non-transparent information. Once the issue is resolved, the review proceeds from the point at which it was suspended.

Therapeutic review: An evidence-based review of publicly available sources regarding a therapeutic category of drugs (e.g., antihypertensive drugs) or a class of drugs (e.g., angiotensin-converting enzyme inhibitors) to support drug reimbursement and policy decisions and encourage the optimization of drug therapy. The scope and depth of the review are determined by jurisdictional needs

Appendix 7: Record of Updates

Table 47: Record of Updates

Version	Date	Summary of revisions
24	Feb. 27, 2025	• Revised procedures for complex and tailored reviews; meetings with industry; revised deliberative process; restructuring project scope description. • Consolidation of the following procedural documents: *Procedures for Time-Limited Reimbursement Recommendations; Non-Sponsored Reimbursement Review Procedures; Therapeutic Review Framework and Process; Procedures for Streamlined Drug Class Reviews; Procedures for Implementation Advice for Health Technologies*
23	Sept. 26, 2024	• Description of the ethics review for complex reviews updated to clarify the domains of ethical considerations explored and the use of summary reports.
22	May 30, 2024	• Revised procedures for provisional funding algorithms. • Integration of procedures for time-limited reimbursement recommendations. • *Procedures for Implementation Advice for Health Technologies* replaced procedure that was previously described within section 12 of this document.
21	May 5, 2024	• Document renamed as Procedures for Reimbursement Reviews. • Revised process for posting of patient group and clinician group input.
20	Jan. 25, 2024	• Revised criteria for the submission of cost-minimization analyses. • Revised description of attendees for reconsideration meetings. • Duration of pipeline meetings extended to 90 minutes. • Clarification added to the confidentiality guidelines.
19	Nov. 30, 2023	• Revised confidentiality guidelines. • Clarification of pharmacoeconomic requirements.
18	Sept. 28, 2023	• Clarification regarding requirements for sponsor summary of clinical evidence. • New application requirement to include responses to requests for deviation from the pharmacoeconomic requirements within the application materials. • Revised procedures for reconsideration meetings to include optional attendance by the participating drug programs. • Updates to section on reassessment through the Therapeutic Review or Streamlined Drug Class Review Processes
17	Jun. 8, 2023	• New instructions and application templates for industry pipeline meetings. • New information in list of included studies provided to the sponsor.
16	Apr. 20, 2023	• New instructions for invitations to observe Health Canada meetings. • Revised timing for calls for patient and clinician group input. • Clarification regarding requirements for sponsor summary of clinical evidence.

Version	Date	Summary of revisions
		• Revisions made based on recommendations from the Procedural Review Panel: • Clarification on the objectives of the reimbursement review process. • Clarification on the descriptions provided for recommendation options. • Revised Appendix 2 to provide further clarity and guidance for those who wish to make a request for a procedural review.
15	Feb. 16, 2023	• Revised instructions for filing and receiving documents. • New application requirement for RIS files with economic references. • Revised process and updated template for ethics review. • Clarification about biosimilar eligibility. • Clarification within the confidentiality guidelines that correspondence between CDA-AMC and the sponsor regarding the drug under review may be shared with authorized recipients.
14	Nov. 10, 2022	• Clarification of pharmacoeconomic requirements.
13	Sept. 1, 2022	• Clarification on notifications following withdrawal from Health Canada. • New information will not be accepted after draft reports issued to sponsor. • Revised naming and eligibility criteria of the Interim Plasma Protein and Related Product review process.
12	Mar. 31, 2022	• New clinical evidence template for sponsors. • Clarification regarding reconsideration process. • Clarification of pharmacoeconomic requirements. • Revised confidentiality guidelines.
11	Dec. 16, 2021	• New rapid provisional funding algorithm process introduced.
10	Nov. 25, 2021	• New complex review process introduced. • New instructions for notifying CDA-AMC when the pause-the-clock process has been implemented during the regulatory review. • Revised process for presubmission meetings. • Clarifications and revisions to pharmacoeconomic requirements.
9	Sept. 16, 2021	• Opportunity for sponsor to review feedback for confidential information. • Revised process regarding new information during the reconsideration phase. • Revisions to pharmacoeconomic requirements. • Revised process for incorporating patient and clinician group input into reports. • Feasibility of adoption listed as a reimbursement condition category.
8	Jun. 17, 2021	• Clarification regarding requests for reconsideration filed by the drug programs. • New application requirement for the status of the drug in other jurisdictions.

Version	Date	Summary of revisions
7	Apr. 29, 2021	• Additional details on requirements for a cost-minimization analysis. • Clarification regarding drug programs to be included in budget impact analysis. • Clarification regarding timelines for the calls for patient and clinician group input. • Revision to the procedural review process. • Reformatted checklists.
6	Mar. 24, 2021	• Revisions to pharmacoeconomic requirements.
5	Feb. 25, 2021	• Revised timelines for posting clinician group input.
4	Jan. 14, 2021	• Revised instructions for submitting advance notification and presubmission meeting request forms to CDA-AMC. • Clarification of pharmacoeconomic submission requirements.
3	Dec. 3, 2020	• Document renamed as Procedures for CADTH Reimbursement Reviews. • Revisions to checklists and file structures for tailored reviews to reflect that the reimbursement status of comparators is no longer located as an appendix of the tailored review submission template.
2	Oct. 29, 2020	• Clinician groups will not be asked to review and validate the summary of input that is prepared by CDA-AMC. • Clarification that the reimbursement status of comparators template must be filed as a Microsoft Word document.
1	Sept. 30, 2020	Original version posted.