CADTH

Procedures for the CADTH Common Drug Review and Interim Plasma Protein Product Review

June 2020

Note: These procedures will be superseded by those described in the *Procedures for CADTH Drug Reimbursement Reviews* for all applications filed with CADTH on or after October 26, 2020. Should you have any questions, please contact **requests@cadth.ca**

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CADTH

Record Of Updates

CADTH Documents	Version	Date
Procedure for Common Drug Review	Original	June 2003
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	6	October 2007
	7	November 2007
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CADTH Documents	Version	Date
Common Drug Review Submission Guidelines for Manufacturers	Original	June 2003
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	12	July 2007
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	1	February 6, 2020
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CADTH

CADTH Contact Information

Table 1: How and Where to Direct Inquiries or Applications

Type of inquiry	How and where to direct
General inquiries regarding CADTH's procedures and processes	**Email:** requests@cadth.ca **Fax:** 613 226 5392 **Mail:** Central Intake CADTH 600-865 Carling Avenue Ottawa, ON K1S 5S8
Filing a submission or resubmission with CADTH	Collaborative Workspaces
Inquiries regarding an active CADTH review	By email to the designated submission coordinator contact provided in the category 1 accepted for review letter
Inquiries regarding CADTH application fees	**Email:** accountsreceivable@cadth.ca

Table 2: Delivery Times

Means of delivery	When considered to have been delivered
By courier, registered mail, regular mail, in person	On the day of receipt by CADTH's reception desk during CADTH business hours (8:00 a.m. to 4:00 p.m. Eastern time)
Email or fax	Between business hours (8:00 a.m. and 4:00 p.m. Eastern time) on the day of transmittal. Note: If sent outside of CADTH business hours, the following business day is considered the date of receipt
Collaborative workspaces	Between business hours (8:00 a.m. and 4:00 p.m. Eastern time) on the day of transmittal. Note: If sent outside of CADTH business hours, the following business day is considered the date of receipt

Abbreviations

BIA	budget impact analysis
CDEC	CADTH Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
CEDAC	CADTH Canadian Expert Drug Advisory Committee
CPEC	CADTH Canadian Plasma Protein Product Expert Committee
DIN	Drug Identification Number
PAC	Pharmaceutical Advisory Committee
FWG	Drug Policy Advisory Committee Formulary Working Group
INESSS	Institut national d'excellence en santé et services sociaux
ITC	indirect treatment comparison
NDS	new drug submission
NOC	Notice of Compliance
NOC/c	Notice of Compliance with conditions
PAG	pCODR Provincial Advisory Group
pCODR	CADTH pan-Canadian Oncology Drug Review
pCPA	pan-Canadian Pharmaceutical Alliance
PTBLC	Provincial and Territorial Blood Liaison Committee
QALY	quality-adjusted life-year
RCT	randomized controlled trial
VBA	Visual Basic for Applications

1. Introduction

1.1 About This Document

The objective of this document is to outline the procedures for two of CADTH's drug reimbursement review processes:

- CADTH Common Drug Review (CDR)
- CADTH Interim Plasma Protein Product Review (PPP).

The procedures for CADTH's pan-Canadian Oncology Drug Review (pCODR) process are currently documented separately and are available on the CADTH website.

This document must be read in conjunction with any relevant issues of the CADTH Pharmaceutical Reviews Update. All references to number of days in this document are in business days unless otherwise specified. Key terms in this document are defined in Appendix 6.

1.2 Overview of the CADTH Drug Review Processes

The objectives of CADTH's drug reimbursement review processes are to reduce duplication across jurisdictions, maximize the use of limited resources, and enhance the consistency of drug reviews. CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, it also issues formulary reimbursement recommendations and/or review reports to all federal, provincial, and territorial drug plans that participate in CADTH's review processes (hereafter referred to as "drug plans").

CADTH's Pharmaceutical Advisory Committee (PAC) provides strategic advice on drug policy issues and drug topics to CADTH. The Formulary Working Group (FWG), Formulary Working Group for Health Technology Assessments (FWG-HTA), and the pCODR Provincial Advisory Group (PAG) have been established to assist PAC in fulfilling its mandate.

The reimbursement recommendations for drugs reviewed through CADTH's drug reimbursement review and therapeutic review processes are provided by one of the following appointed, national, expert advisory committees:

- The Canadian Drug Expert Committee (CDEC) is used for drugs that are reviewed through CADTH's CDR process.
- The Canadian Plasma Protein Product Expert Committee (CPEC) is used for products that are reviewed through the PPP process.
- The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) is used for drugs that are reviewed through CADTH's pCODR process.

Each committee is composed of individuals with expertise in drug therapy, drug evaluation, and drug utilization, and public members who bring a lay perspective. The current committee members are listed on the CADTH website. It is important to note that CADTH's recommendations are non-binding to the drug plans. Each drug plan makes its own reimbursement decisions based on the CADTH's recommendation in addition to other factors, including the plan's mandate, jurisdictional priorities, and financial resources.

1.3 Changes to These Guidelines

CADTH may amend the *Procedures for the CADTH Common Drug Review and Interim Plasma Protein Product Review* and all matters related to its drug reimbursement review processes. CADTH may request stakeholder feedback for procedural changes and the drug programs are consulted, as required. Amendments to, and clarifications of, the *Procedures for the CADTH Common Drug Review and Interim Plasma Protein Product Review* and all related documents may be effected by means of directives (called *CADTH Pharmaceutical Reviews Update*) as issued by CADTH on an as-needed basis between revisions of these documents.

1.4 Interaction Between CADTH and the Sponsor

Once an application has been filed, CADTH 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, CADTH is unable to offer conference calls to sponsors who have questions regarding the CDR or PPP processes, and encourages sponsors who have questions to submit a written inquiry to requests@cadth.ca. A written response will be provided in a timely manner. With the exception of pre-submission meetings, in-person meetings will not be offered.

Direct contact between a sponsor and members of CADTH's expert review committees (in their capacity as members of the expert review committees) or the CADTH review team is not permitted during the review process. Direct approaches in any form to committee members or the CADTH 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 a member of the expert review committee or member(s) of the CADTH 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 a submission or resubmission on behalf of a sponsor are required to copy an official contact for the sponsor on all email correspondence with CADTH. CADTH will not respond to any email correspondence from a consultant if an official contact for the sponsor has not been copied.

1.5 CADTH Confidentiality Guidelines

CADTH has developed confidentiality guidelines to protect confidential information obtained through the CDR or PPP 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. CADTH will comply with these confidentiality guidelines when handling information as part of the CDR or PPP processes. A sponsor will be deemed to have consented to the confidentiality guidelines when it files a submission or resubmission, or when it supplies other information to CADTH. A sponsor will maintain the confidentiality of documents shared with it by CADTH. The confidentiality guidelines will constitute an agreement between CADTH and the sponsor.

2. Eligibility for Drug Reimbursement Review Processes

2.1 Eligible Submissions

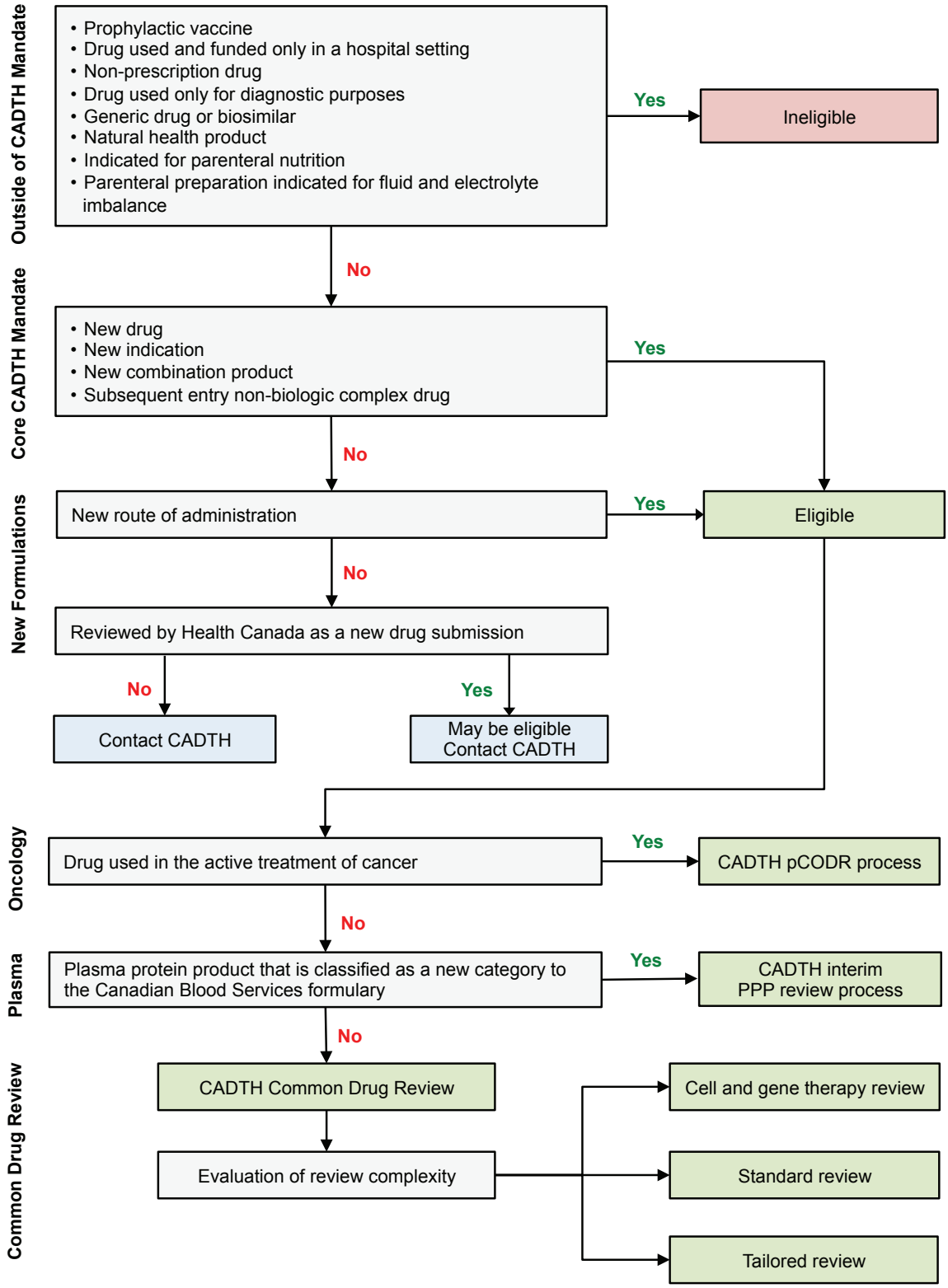
This section provides guidance regarding eligibility for the majority of submissions. In some situations, CADTH may consult with drug plans to confirm eligibility of a drug and make a decision on a case-by-case basis. Sponsors that have questions regarding whether or not a drug is eligible for review through the CDR, pCODR, or PPP processes are asked to complete an eligibility request form and submit it to requests@cadth.ca. Eligibility should be determined before requesting a pre-submission meeting or providing advanced notification.

A sponsor or the drug plans may file a submission for a new drug, a drug with a new indication, or a new combination product 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. Table 3 provides an overview of each eligible submission type.

Table 3: Drugs Eligible for CADTH's Drug Reimbursement Review Processes

Product type	Description
New drug	• A new active substance that has not been previously marketed in Canada.
Drug with a new indication	• A drug previously reviewed by CADTH that has received or is seeking approval from Health Canada for use in a new indication. • A drug marketed before the establishment of CADTH's drug reimbursement review processes that has received or is seeking approval from Health Canada for use in a new indication. • A drug previously reviewed by CADTH that has received or is seeking approval from Health Canada for use in a new age group of patients.
New combination product	• Two or more drugs that have not been previously marketed in Canada in that combination.
New formulation of an existing drug	• New formulations of existing drugs that have a different route of administration than formulation(s) previously reviewed by CADTH.
Plasma protein product	• A drug that is classified as a new category to the Canadian Blood Services formulary: 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.
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.

Figure 1: Drugs Eligible for Review Through the CADTH Drug Reimbursement Review Processes



pCODR = CADTH pan-Canadian Oncology Drug Review; PPP = plasma protein product.

2.1.1 New Drug

A new drug, for CADTH's 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 the CDR process 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 by CADTH in consultation with the drug plans on a case-by-case.

All submissions for new drugs undergo a standard review.

2.1.2 New Indication

A drug with a new indication is:

- a drug previously reviewed through CADTH's CDR or pan-Canadian Oncology Drug Review processes that has received an NOC or NOC/c for a new indication
- an active substance marketed before the establishment of CDR (in September 2003) that has received an NOC or NOC/c for a new indication
- a drug previously reviewed through the CDR process that is approved for use in a new patient population age range.

All submissions for drugs with a new indication undergo a standard review.

2.1.3 New Combination Product

A new combination product consists of two 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. Sponsors who are planning to file a submission for a new combination product are required to complete and submit a tailored review application form to CADTH (requests@cadth.ca) before filing the submission. CADTH will review the information and, with input from the drug plans (as needed), confirm whether a standard or tailored review should be filed. CADTH will typically provide a response within 10 business days of receiving the form.

2.1.4 New Formulations of Existing Drugs

A new drug for the purposes of a CADTH 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 CADTH's drug reimbursement review processes and/or are currently being funded by the drug plans for the same indication (note: these are considered line extensions by CADTH):

- a new non-parenteral dosage form with the same route of administration, as long as 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., intravenous, intramuscular, subcutaneous dosage forms) are not considered line extensions of one another by CADTH, 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 CADTH (requests@cadth.ca) for guidance on whether a submission to CADTH is required for a new parenteral formulation. Sponsors who are planning to file a submission for a new formulation are required to complete and submit a tailored review application form to CADTH (requests@cadth.ca) before filing the submission. CADTH will review the information and, with input from the drug plans (as needed), confirm whether a standard or tailored review should be filed. CADTH will typically provide a response within 10 business days of receiving the form.

2.1.5 Plasma Protein Products

Submission for new categories to the Canadian Blood Services formulary will be assessed by Canadian Blood Services and CADTH using the current Canadian Blood ServicesPlasma Protein Product selection eligibility criteria, subject to approval by the provincial and territorial governments (excluding Quebec) for a new category on the Canadian Blood Services formulary. The current 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
- is not carried in the health system already.

Canadian Blood Services and CADTH will initiate a review 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 on the Canadian Blood Services formulary, or
- whether the product would be reviewed by Canadian Blood Services as a new brand within an already approved category on the Canadian Blood Services formulary.

Sponsors making product submissions with questions regarding whether or not a product is eligible for review through the interim process are asked to complete an eligibility request form and submit it to requests@cadth.ca. CADTH will forward the information to Canadian Blood Services for discussion with the PTBLC. Eligibility should be determined before requesting a pre-submission meeting or providing advance notification.

2.1.6 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 CADTH before filing a submission for a subsequent-entry non-biological complex drug (requests@cadth.ca).

2.2 Eligible Resubmissions

A resubmission is a review of any drug that has previously been reviewed by CADTH and for which a final recommendation has been issued. Resubmission eligibility must be determined before requesting a pre-submission meeting or providing advanced notification to CADTH (Figure 2).

2.2.1 New Information

A resubmission based on new information consists of one or both of the following:

- new clinical information in support of improved efficacy or safety
- new cost information that significantly affects the cost-effectiveness of the drug.

Any new studies included in the resubmission must address the specific issues identified by the expert review committee in the final recommendation document. Table 4 summarizes the supporting information that must be filed for resubmissions.

Table 4: Summary of New Information Required for Resubmissions

Basis of resubmission	Supporting information that must be filed
New clinical information supporting improved efficacy or safety	• One or more new studies that address specific issues identified by the expert review committee in the final recommendation document • New pharmacoeconomic evaluation • New budget impact analysis (category 2 requirement)
New cost information that significantly affects the cost-effectiveness of the drug	• New pharmacoeconomic evaluation • New budget impact analysis (category 2 requirement)

Although not always a requirement, CADTH considers new evidence from one or more randomized controlled trials (RCTs) to be the preferred form of new clinical information for resubmissions based on improved efficacy and/or safety. CADTH considers data from non-randomized studies to be particularly useful in the following situations:

- when the evaluation of important clinical end points and rare adverse events requires longer-term follow-up
- when there is uncertainty regarding the persistence of efficacy of the drug under review because of short-term clinical trials
- when an RCT is impractical because of a limited number of patients
- when it is considered unethical to conduct an RCT
- when randomized studies lack relevant comparators (e.g., an indirect comparison is conducted to evaluate the comparative efficacy and safety of the drug under review relative to appropriate comparators)
- when there is uncertainty regarding the dosage of the drug(s) under review that is used in actual clinical practice
- when the RCTs have limited external validity and additional non-randomized studies could provide meaningful insight into the effectiveness of the treatment in the target population.

2.2.2 Eligibility Assessment for Resubmissions

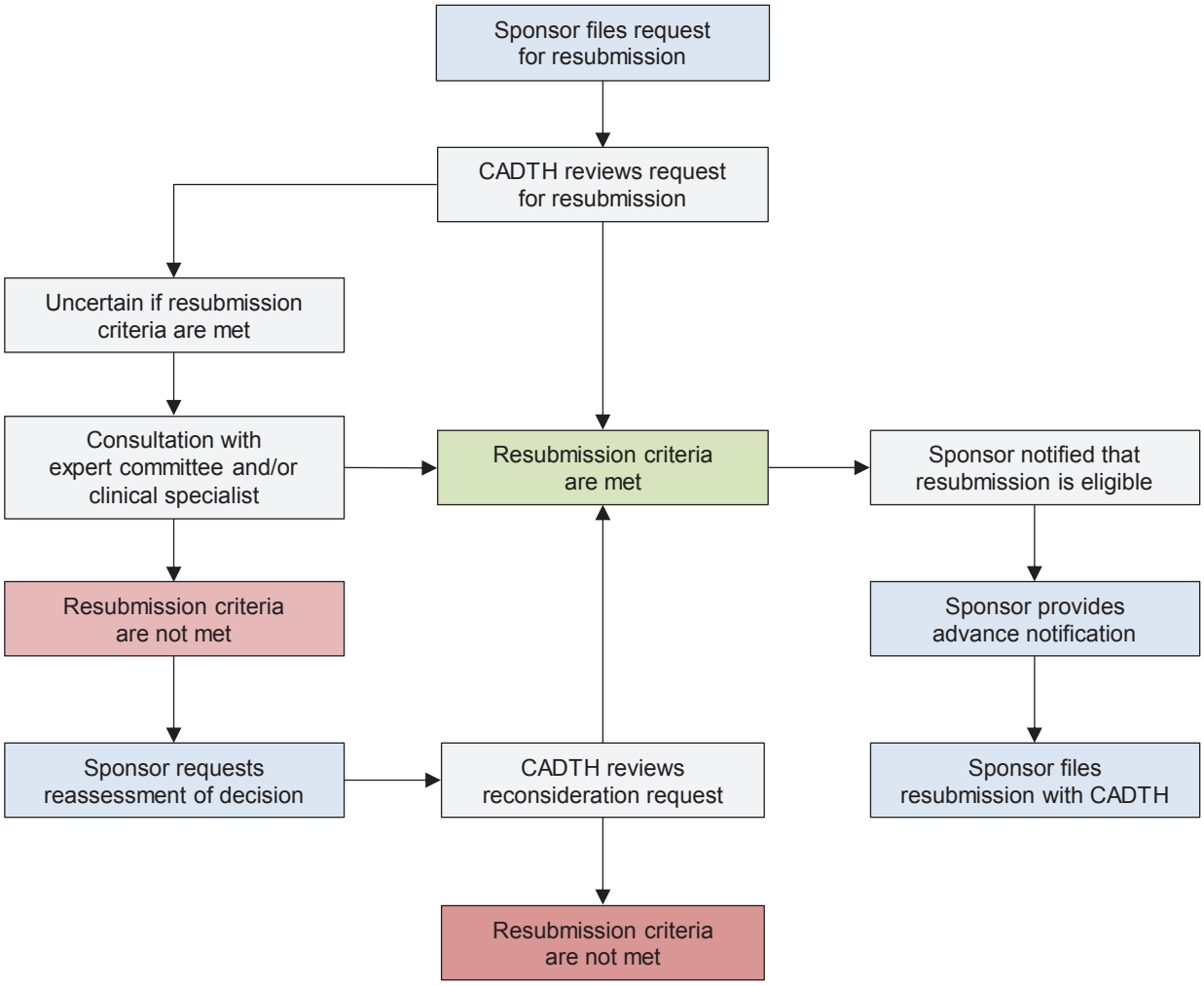
- Before filing a resubmission, sponsors are required to have its eligibility assessed by CADTH. Sponsors must provide the following information to requests@cadth.ca for evaluation by CADTH:
  - a completed resubmission eligibility form
  - copies of one or more new studies that address specific issues identified by the expert review committee in the final recommendation document.
- CADTH will screen the information provided by the sponsor to determine if:
  - the information provided by the sponsor represents new information
  - the (one or more) new studies provided by the sponsor address specific issues identified by the expert review committee in the final recommendation document.
- CADTH may consult with members of the expert review committee and/or clinical experts to determine if the new information filed by the sponsor addresses the issues noted in the previous recommendation. However, the final decision regarding whether or not a resubmission will be eligible for review will be determined by CADTH.
- CADTH's assessment of eligibility will typically be completed within 10 business days. Sponsors will be notified by CADTH if additional time is required to complete the assessment.
- If CADTH determines that the sponsor's resubmission comprises new information and contains at least one study that addresses the specific issues identified by the expert review committee in the final recommendation document, the sponsor will be apprised in writing that the resubmission is eligible for review.
- If CADTH determines that the sponsor's resubmission does not comprise new information or does not address the specific issues identified by the expert review committee in the final recommendation document, the sponsor will be apprised in writing that the resubmission is not eligible.
- When a sponsor has been informed by CADTH that a resubmission is not eligible, the sponsor may file one written request for the decision to be reassessed by CADTH. The request for reassessment must clearly outline why the sponsor disagrees with CADTH's decision.
- Sponsors have 10 business days to file a request for reassessment after receiving notification from CADTH regarding the eligibility of a resubmission.
- Sponsors will only be entitled to have the eligibility decision reassessed once.
- CADTH will examine the reassessment request to determine whether the issue(s) raised change the conclusions regarding the eligibility of the resubmission. CADTH may consult with members of the expert review committee and/or clinical experts (as required). The final decision regarding whether or not a resubmission is eligible for review will be determined by CADTH.
- CADTH's consideration of each request for reassessment will typically be completed within 10 business days. Sponsors will be notified by CADTH if additional time is required to complete the assessment.
- CADTH will apprise the sponsor in writing of the final decision regarding eligibility of the resubmission.
- CADTH will post the results of the resubmission eligibility assessment on the CADTH website.

- CADTH will retain and dispose of documents associated with the resubmission in accordance with the *CADTH Confidentiality Guidelines for the Common Drug Review and Interim Plasma Protein Product Review*.
- All completed resubmission eligibility assessments may be shared by CADTH with the federal, provincial, territorial governments (including their agencies and departments) and the pan-Canadian Pharmaceutical Alliance (pCPA) office.
- After receiving confirmation from CADTH that the proposed resubmission is eligible for review by CADTH, sponsors are required to provide CADTH with advance notification for the pending resubmission. Advance notification for resubmissions must be provided in accordance with section 3.2.

2.2.3 Volume of Resubmissions

To ensure fair access to CADTH's review process for new drug submissions, CADTH may limit the number of resubmissions that can be made and/or initiated within a defined period of time. This decision will be made by CADTH based on the availability of resources, and will be communicated to stakeholders through a *CADTH Pharmaceutical Reviews Update*.

Figure 2: Assessing the Eligibility of Resubmissions



2.3 NOC Status at the Time of Filing the Submission

A submission can be filed on either a pre-NOC or a post-NOC basis (Table 5).[1]

Table 5: NOC Status at the Time of Filing

NOC status	Description
Pre-NOC	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 CADTH holiday, the next business day will be used. 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 finalized because the embargoed recommendation will not be released until all required information, including a copy of the NOC or NOC/c, has been received by CADTH.
Post-NOC	A submission may be filed on a post-NOC basis after the drug has been granted an NOC or NOC/c by Health Canada for the indication(s) to be reviewed by CADTH.

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

2.4 Types of Reviews

Table 6 summarizes the type of CADTH review conducted for the different submission and resubmission categories. The following types of reviews are currently conducted by CADTH:

- A standard review consists of CADTH conducting a systematic review of clinical evidence provided by the sponsor along with studies identified through its independent, systematic literature search, and an appraisal of the sponsor-provided pharmacoeconomic evaluation.
- A tailored review consists of the CADTH conducting an appraisal of the clinical evidence and pharmacoeconomic evaluation filed by the sponsor using a CADTH-provided review template.
- A cell and gene therapy review is conducted in a manner similar to a standard review, but involves additional review and consideration of potential implementation issues and ethical challenges.
- A request for advice is used to address questions related to changes in contextual factors that may affect the ability of the participating jurisdictions to implement existing recommendations from CADTH's expert review committees.
- Resubmissions are conducted when new evidence is available for drugs that have previously been reviewed by CADTH for the indication of interest and for which a final recommendation has been issued.

[1] Pre-NOC also includes pre-NOC/c and post-NOC includes post-NOC/c submissions.

Table 6: CADTH Review Types

Review type	Application
Standard review	Submission for a new drug Submission for a drug with a new indication Submission for a new combination product (selected)
Tailored review	Submissions for new combination products or new formulations of existing drugs that CADTH has designated as tailored reviews Submissions for subsequent-entry non-biologic complex drugs
Cell and gene therapy review	Submissions for cell and gene therapies
Resubmission	Drugs that have previously been reviewed by CADTH for the indication of interest and for which a final recommendation has been issued
Request for advice	Changes in contextual information that may affect the ability to implement existing CADTH recommendations

2.5 Requests for Advice

Drug plans may file a request for advice regarding a previous final recommendation issued by CADTH. The request for advice must be provided to CADTH in a signed letter that clearly describes the issues of interest to the drug plans.

2.6 Drug Plan-Initiated Submissions and Resubmissions

Drug plans may file a submission or resubmission through CADTH's ddrug reimbursement review process. The submission or resubmission must be filed with CADTH in a signed letter that clearly describes the issues of interest to the drug plans. For these submissions and resubmissions, CADTH supports the drug plans by obtaining and compiling information to conduct the review. CADTH will contact the manufacturer (i.e., the holder of the Drug Identification Number [DIN]) and provide an opportunity to share relevant clinical and pharmacoeconomic data. In general, the review process for a drug plan–filed submission or resubmission will be the same as that used in the review of a submission or resubmission filed by a sponsor.

2.7 Declining to File a Submission With CADTH

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

- Jurisdictions determine that they require a recommendation from CADTH to inform their reimbursement decisions.
- CADTH will issue a letter to the manufacturer on behalf of the Formulary Working Group (FWG) or pCODR Provincial Advisory Group (PAG) informing it that the drug is eligible for review through the CDR, PPP, or pCODR processes and that the plans would like a submission to be filed with CADTH.
- The manufacturer will have 30 business days to respond to the FWG or PAG Chair indicating whether or not it is planning to file a submission for the drug, as well as its anticipated timelines if it is choosing to submit.

- In the following scenarios a statement will be issued on the CADTH website indicating that "CADTH is unable to recommend reimbursement as a submission was not filed by the manufacturer":
  - a manufacturer indicates that they are 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 CADTH's expert review committees.
- The proposed changes to the procedure will only apply to submissions and not to resubmissions.
- If CADTH has issued a statement on the basis that a submission was not filed, the manufacturer may file a submission at any point in the future in accordance with CADTH's procedures. This would result in a CADTH recommendation being issued for the drug and the previous statement being removed from the website.
- The participating jurisdictions can continue to file drug plan-initiated submissions provided the submission requirements can been addressed (e.g., provision of an economic model and pharmacoeconomic evaluation).

2.8 Eligible Drugs That Have Become Genericized

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

Circumstances that would likely not require a submission to be filed with CADTH 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 participating drug plans 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 participating drug plans (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 participating drug plans (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 with CADTH 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 CADTH may advise a manufacturer 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 may contact CADTH at any time (requests@cadth.ca).

3. Pre-Submission Procedure

3.1 Pre-Submission Meetings

Pre-submission meetings are offered to facilitate the efficient preparation and filing of submissions and resubmissions with CADTH. The pre-submission meeting provides the opportunity for CADTH staff and the sponsor to discuss the upcoming submission or resubmission. The goal of the meeting is to assist sponsors in improving the quality, relevance, and clarity of the information filed for review by CADTH. The meeting is not meant to be consultative in nature, outside of clarifying procedural and/or submission or resubmission requirements. This is because at the time of a pre-submission meeting, CADTH has not reviewed the submission or resubmission requirements, and therefore is not in a position to provide final advice on a submission or resubmission. Any information and advice provided by CADTH at the pre-submission meeting will be non-binding.

Pre-submission meetings are scheduled for a maximum of one hour and sponsors are limited to one meeting per drug submission or resubmission. The meeting is held at the CADTH office in Ottawa; however, a teleconference option is available for those unable to attend in person. Sponsors may bring consultants and/or clinical experts as representatives. Representatives from the participating drug plans and pCPA may attend pre-submission meetings. CADTH may record pre-submission meetings for internal purposes.

Once a submission or resubmission has been filed with CADTH, it is no longer eligible for a pre-submission meeting.

Sponsors may request a pre-submission meeting with CADTH for a submission or resubmission to be filed within 12 months of the meeting. To ensure maximum value from the discussion, sponsors are encouraged to schedule the pre-submission meeting at least 20 business days before the anticipated filing date of the submission or resubmission. To request a pre-submission meeting, sponsors are required to complete a Pre-submission Meeting Request Form and submit it to CADTH (meetingrequests@cadth.ca).

3.2 Advance Notification Procedure

Sponsors are required to provide CADTH with a minimum of 30 business days of advance notice for anticipated submissions and resubmissions. All sponsors are encouraged to provide CADTH with as much notice as possible to facilitate resource planning and budgeting (≥ 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 CADTH Common Drug Review Advance Notification Form in its entirety and submit it to CADTH (requests@cadth.ca). The 30–business day notification period will be counted from the date of receipt of the advance notification form to the targeted filing date for all anticipated submissions.

Information provided to CADTH 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, sponsors are required to receive confirmation from CADTH that the proposed resubmission is eligible for review, before providing advance notification (see section 2.2). The eligibility assessment and advance notification processes have to occur sequentially to ensure that the patient engagement process is only initiated for eligible resubmissions.

Sponsors who provide notification of more than 30 business days in advance of the anticipated date of filing are required to confirm the anticipated filing date 30 business days in advance (Table 7). Information regarding a pending submission or resubmission will be posted on the CADTH website at the time the call for patient input is issued (i.e., 20 business days before the anticipated filing date).

Table 7: Advance Notification Process for Submissions and Resubmissions

Advance notification process	Days before anticipated filing date
CADTH 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 input issued	20 business days

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

A sponsor is required to advise CADTH by email (requests@cadth.ca) of changes in the anticipated date of filing a submission or resubmission as soon as possible. For changes to an anticipated filing date made before posting the pending submission or resubmission on the CADTH website and issuing the call for patient input, the timelines will be adjusted based on the new anticipated filing date. For changes to an anticipated filing date made after the pending submission or resubmission has been posted on the CADTH website, and the call for patient input has been issued, the call for patient input will remain open for a total of 35 business days. CADTH 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 determining CADTH resourcing and timelines. Submissions and resubmissions received at CADTH earlier than the confirmed anticipated filing date will be held and considered received only on the anticipated filing date.

3.3 Health Canada Information Sharing

- As described in *Notice to Industry: Aligned Reviews Between Health Canada and Health Technology Assessment Organizations*, an optional information sharing process has been established to permit Health Canada and CADTH to exchange information regarding the drug under review, for submissions filed with CADTH on a pre-NOC basis. Participation in this process could ensure that CADTH has advance notice of any issues that have the potential to impact CADTH's review of the drug (e.g., changes to the indicated patient population), potentially avoiding delays in the issuance of CADTH's recommendation.
- Sponsors must indicate on the advance notification form (i.e., received ≥ 30 business days in advance of the submission filing date) whether or not they have consented or will be consenting to participate in the information sharing process with Health Canada.
- To promote alignment of regulatory and CADTH reviews, sponsors should consent to information sharing at the time of, or before, submission filing with Health Canada. This may help to minimize the time between issuance of market authorization and CADTH's recommendation.

- If the sponsor is unwilling to participate in the information sharing process with Health Canada, CADTH will continue to request information directly from the sponsor.
- The CADTH Collaborative Workspaces will be used to exchange documents between Heath Canada and CADTH.
- In the interest of transparency, CADTH will indicate whether or not a sponsor has consented to participate in the information sharing process (if applicable).

4. Stakeholder Engagement

CADTH follows strict processes to independently and objectively evaluate evidence. It is inappropriate and unhelpful to the process for 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.

4.1 Patient Engagement

Patient 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 by CADTH in the review of submissions, resubmissions based on new clinical information, and requests for advice, and by the expert review committee in the development of recommendations.

4.1.1 Call for Patient Input

- The call for patient input regarding a submission or resubmission is posted 20 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 by CADTH.
- Patient groups have a total of 35 business days for preparing and submitting patient input.
- Open calls for patient input are available via:
  - the CADTH website (as a pending drug submission and an open call for patient input)
  - E-Alerts to all subscribed patient groups (patient groups can subscribe to E-Alerts by using the "subscribe" option on the CADTH website)
  - CADTH Twitter accounts: English, @CADTH_ACMTS and French, @ACMTS_CADTH
- If a pending submission or resubmission is delayed following the issuance of the call for patient input, CADTH may re-post the call for patient input if the delay is six months or longer. This is undertaken for two 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 CADTH's review process.

4.1.2 Submitting Patient Input

- Patient input is submitted to CADTH 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 to CADTH. CADTH will accept patient input from individual patients and caregivers only 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 CADTH (requests@cadth.ca) to confirm the absence of a relevant patient group. Upon confirmation that no relevant patient group exists, CADTH will provide interested individuals with the individual patient and caregiver template for completion. The process for providing input, and how CADTH uses and posts that input, 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 CADTH 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 review committee in their work.
- Patient groups must submit their input as a Microsoft Word document by the posted deadline date for the information to be used by CADTH.

4.1.3 How Patient Group Input Is Used

- All patient group input received for the drug under review is collated and summarized by CADTH. The approximately two-page summary is sent to each of the submitting patient groups for their review and comments. Patient groups are asked to comment on whether the summary reflects the main issues and outcomes of importance to them and to ensure that no private information is included in the summary. A period of up to five business days is allotted for patient group to provide comments on the summary document. The patient group input summary is incorporated into CADTH's report(s).
- For all submissions, resubmissions, and requests for advice for products patient group input is used by CADTH in the development of the review protocol. The patient group input summary and the patient group input submissions in their entirety are included in the committee brief. Public members of the expert committee present the patient input at the outset of the committee's deliberations (section 8.3), and a summary of the patient input discussion is included in the committee's recommendation.
- All patient input submissions are kept on file and may be referred to in future CADTH reviews of the same drug or other drugs with similar indications.

4.1.4 Posting Patient Group Input

- CADTH will include the names of the patient groups who provided input within the key milestone table on the CADTH website. The information will be posted for the drug under review after the call for patient input is closed.
- The patient group submissions for each drug are consolidated for posting on the CADTH website. Posting will typically occur within two weeks after the call for patient input has been closed.
- The conflict of interest information will be included in the posted material.
- CADTH 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 input submitted.

4.2 Clinician Engagement

4.2.1 Role of Clinical Experts

- All CADTH review teams include at least one clinical specialist with expertise regarding 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., providing guidance on the development of the review protocol; 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.

- In the case of drugs that are undergoing or have undergone an expedited review by Health Canada for the indication of interest (i.e., priority review or advance consideration under an NOC/c), multiple experts will be incorporated into the review team and supplemental clinical panels may be convened during the review to inform the committee's recommendation and/or after the review to provide implementation support to the participating drug plans (section 4.2.3). At the request of the participating drug plans, CADTH may also convene clinical panels for selected drugs that have not undergone an expedited review by Health Canada.

4.2.2 Call for Clinical Experts

- CADTH issues a *Call for Clinical Experts* for the purposes of identifying clinical experts who are interested in working with CADTH. This call will be issued at the same time the call for patient input is currently posted (i.e., 20 business days before the anticipated date of receipt). Those interested will be asked to register by completing a web form with contact information and details about their areas of expertise and interest. CADTH will compile a database of registered clinicians and use this information to assist in the recruitment of clinical experts.
- CADTH will review the information provided by registrants and selected individuals may be contacted to discuss their potential participation in the review.
- In addition to the review-specific calls for clinical experts that will be issued for the CDR or PPP processes, CADTH encourages any interested clinicians to register for potential involvement in future CADTH opportunities, including initiatives through our Optimal Use and Therapeutic Review processes.
- The following factors are considered by CADTH 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 CADTH's review timelines
  - Regional representation (particularly for clinical panels)

4.2.3 Clinical Panels

Eligibility and Function

- CADTH may establish clinical panels for drugs that are undergoing or have undergone an expedited review by Health Canada for the indication of interest (i.e., priority review or advance consideration under a NOC/c). CADTH will also consider requests from the participating drug plans to initiate a clinical panel for a drug that did not undergo an expedited review. 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 potential place in therapy of the drug (e.g., potential reimbursement conditions).
- 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 submission or resubmission is accepted for review by CADTH.

CADTH and INESSS Joint Engagement

- CADTH and Institut national d'excellence en santé et services sociaux (INESSS) may jointly engage with clinical experts on selected drug products.
- CADTH and INESSS will collaborate to establish the clinical panels, interact with the clinical experts on the panels, and summarize input and key information from the clinical panellists.
- CADTH and INESSS independently complete all other phases of their respective review process, including the deliberation and recommendation phases.
- Drugs will be selected jointly by CADTH and INESSS and will typically involve the following characteristics:
  - Similar submission timelines to CADTH and INESSS
  - Challenges in generating robust evidence due to the rarity of the condition
  - Potential for challenging implementation issues
  - Perceived ethical challenges for decision-makers
  - High acquisition costs and/or substantial budget impact.
- CADTH and INESSS will select drugs based on the above noted considerations and will notify the sponsor in writing. It is important to note the following:
  - The decision to consider drugs for joint engagement will be made solely at the discretion of CADTH and INESSS.
  - Sponsors cannot request or apply to have a drug considered for joint engagement by CADTH and INESSS.
  - Participation in the joint engagement process will not be optional for the sponsors of the drugs identified by CADTH and INESSS.
  - Drugs selected for joint engagement will be identified in the review documentation posted on the CADTH and INESSS websites.

Panel Composition

- The panels will comprise clinical experts with experience in the diagnosis and management of the condition for which the drug under review is indicated. Whenever possible, CADTH will seek to obtain representation from across Canada. Potential experts will be identified by CADTH. The number of clinical specialists included on the panels may vary based on input from the participating jurisdictions 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 review committee members (i.e., chairs and lead discussants), and CADTH staff (i.e., review team members). If the drug is being reviewed through the CADTH-INESSS joint engagement process, staff from INESSS as well as members of their expert review committee will also attend the clinical panel meetings.

Input from Clinical Panels

- The activities of the clinical panels will occur before the expert review committee meeting to ensure that the committee has this information available to inform their deliberation and recommendation.

- The outcome of these panel meetings will be made available to the sponsor for review and commentary before the expert review committee meeting. CADTH will aim to integrate the input of the clinical panel into the review report(s) before being sent to the sponsor for review and commentary.
- The reports will still be sent to the sponsor for comment in the event CADTH is unable to integrate the clinical panel's findings into the draft review report(s) 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 panel's findings for review and commentary in a separate distribution as soon as possible. CADTH will notify the sponsor if there are any anticipated delays regarding these steps in the process.
- Any feedback from the sponsor regarding the input from the clinical panel will be reviewed and addressed by CADTH and the clinical experts (as required). The review report(s) will be revised as CADTH deemed appropriate.
- The input from the clinical expert panel will be made available to the expert review committee for their deliberations on the drug under review (section 8).

4.3 Drug Plan Engagement

4.3.1 Role of the Drug Plans

- The participating drug plans provide input on each drug being reviewed through the CDR or PPP processes by identifying issues that may impact their ability to implement a recommendation.
- This input increases the relevance of the recommendations and can potentially avoid the need for a request for clarification 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 of comparator drugs across the participating jurisdictions
  - Potential for combination use with other available therapies
  - Potential for increasing the dosage over time
  - Consistency with previous CADTH recommendations for similar drugs
  - Potential issues with administration or distribution mechanisms (e.g., need for specialty clinics)
  - Challenges with diagnostic testing requirements

4.3.2 Input From Drug Plans

- For each drug review, a lead jurisdiction is assigned by CADTH using a rotational schedule of FWG members.
- The lead jurisdiction considers the information regarding the drug under review and prepares a summary of potential implementation considerations. This summary is presented and discussed with the other FWG members before each expert review committee meeting.
- The summary of implementation issues is then made available to all expert review committee members to inform their deliberations. In the event the expert review committee has questions regarding any potential implementation issues associated with a recommendation, the chair may ask the drug programs to provide clarity for the committee.

5. Requirements for Submissions and Resubmissions

- The submission requirements for all eligible submission types are grouped into the following categories:
  - category 1 requirements
  - category 2 requirements
  - additional information.
- A brief description of these requirements is provided in Table 8 and detailed descriptions are provided in subsequent sections.
- For all submission types, the clinical and pharmacoeconomic information provided in the category 1 and category 2 requirements should focus on the indication(s) to be reviewed under the CDR or PPP processes (unless otherwise specified).
- The submission checklists for category 1 and category 2 requirements can be found in Appendix 3. These checklists may assist sponsors in ensuring that all requirements have been included in the submission.
- To expedite screening and for efficient use of documents throughout the review, sponsors must organize all submission information in the order prescribed in the category 1 and category 2 requirements below and follow the electronic file folder format in Appendix 4.

Table 8: Submission Requirement Categories

Requirement category	Function in CADTH's process	Due
Category 1	Used by CADTH and the expert review committee for the review and recommendation process	At the time of filing the application
Category 2	Used by the drug plans and not considered as part of CADTH's review or recommendation processes. CADTH provides secretariat support to the drug plans by ensuring that category 2 requirements have been filed	≤ 20 business days from the date the submission or resubmission was accepted for review
Additional information	Additional information that CADTH may require for completion of the review (e.g., Clinical Study Reports or Health Canada Reviewer's Report[s])	As soon as possible following a request by CADTH, to avoid delays in the review process

5.1 Category 1 Requirements

- Category 1 requirements are used by CADTH and the expert review committee during the review and recommendation process.
- One copy of all category 1 requirements must be filed with CADTH as a single submission package and accepted for review by CADTH before it is initiated.
- The category 1 requirements for standard reviews and tailored reviews are summarized in Table 9 and the category 1 requirements for resubmissions are summarized in Table 10.
- Detailed descriptions of the information that comprise the category 1 requirements for submissions are described below. Specific requirements for a submission filed on a pre-NOC versus post-NOC basis are delineated in the descriptions that follow the table.
- The sponsor is responsible for ensuring that appropriate copyright permissions have been obtained for electronic copies of articles included in category 1 requirements of a submission, to be shared among CADTH, the expert review committee, and the drug programs for the review of the submission.

Table 9: Category 1 Requirements for Submissions

Section	Specific items and criteria	Common Drug Review			Plasma protein product
		Standard	Cell or gene	Tailored	
General information	• Completed application overview template	Required	Required	Required	Required
	• Signed cover letter	Required	Required	Required	Required
	• Completed executive summary template for a submission	Required	Required	Required	Required
	• Product monograph	Required	Required	Required	Required
	• Completed declaration letter template	Required	Required	Required	Required
Submission template	• Completed tailored review submission template	Not applicable	Not applicable	Required	Not applicable
Health Canada documentation	• NOC or NOC/c and Letter of Undertaking, or • A placeholder document specifying anticipated NOC date	Required	Required	Required	Required
	• Table of Clarimails or Clarifaxes	Required	Required	Required	Required
Efficacy, effectiveness, and safety information	• Common Technical Document sections 2.5, 2.7.1, 2.7.3, 2.7.4, and 5.2, or a statement indicating any section(s) are not available	Required	Required	Required	Required
	• Reference list and copies of key clinical studies and errata	Required	Required	Required	Required
	• Clinical study reports for pivotal and key clinical studies	Required if filed on or after March 2, 2020			
	• Table of studies	Required	Required	Required	Required
	• Reference list and copies of editorial articles	Required	Required	Not required	Required
	• Reference list and copies of new data	Required	Required	Not required	Required
	• Reference list and articles for validity of outcomes	Required	Required	Not required	Required
	• Indirect comparison with full technical report	May be required	May be required	Not required	May be required
Economic information	• Pharmacoeconomic evaluation for the full population identified in the indication(s) to be reviewed by CADTH	Required	Required	Not required	Required
	• Unlocked and fully executable economic model	Required	Required	Not required	Required
	• Economic model supporting documentation	Required	Required	Not required	Required

Section	Specific items and criteria	Common Drug Review			Plasma protein product
		Standard	Cell or gene	Tailored	
Budget impact analysis	• Aggregate pan-Canadian budget impact report	Required if filed on or after March 2, 2020	Required	Required if filed on or after March 2, 2020	Required
	• Aggregate pan-Canadian budget impact model		Required		Required
	• Supporting documentation used in budget impact analysis		Required		Required
Reimbursement status of comparators	• Completed template listing the reimbursement status of all relevant comparators	Required if filed on or after March 2, 2020			
Epidemiologic information	• Disease prevalence and incidence data	Required	Required	Required	Required
	• Number of patients accessing a new drug	May be required	May be required	May be required	May be required
Pricing and distribution information	• Submitted price per smallest dispensable unit to four decimal places	Required	Required	Required	Required
	• Method of distribution	Required	Required	Required	Required
Implementation plan	• Completed implementation plan template	Not required	Required	Not required	Not required
Companion diagnostics	• Reference list and articles focused on clinical utility	May be required	May be required	May be required	May be required
	• Disclosable price	May be required	May be required	May be required	May be required
Pre-NOC letter	• Letter for sending NOC or NOC/c to CADTH	Required	Required	Required	Required

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

Table 10: Category 1 Requirements for Resubmissions

Section	Specific items and criteria	Resubmission type	
		New clinical and cost	New cost only
General information	• Completed application overview template	Required	Required
	• Signed cover letter	Required	Required
	• Completed executive summary template for a resubmission	Required	Required
	• Product monograph	Required	Required
	• Completed declaration letter	Required	Required
New efficacy and/or safety information	• Reference list and copies of new clinical studies and errata	Required	Not required
	• Reference list and copies of editorial articles	Required	Not required
	• Reference list and articles for validity of outcome measure	Required	Not required
	• Updated table of studies	Required	Required
	• Clinical study reports for new clinical studies	Required if filed on or after March 2, 2020	
Economic information	• New pharmacoeconomic evaluation for the full population identified in the indication(s) to be reviewed by CADTH	Required	Required
	• Unlocked and fully executable economic model	Required	Required
Epidemiologic information	• Disease prevalence and incidence data	Required	Required
Reimbursement status of comparators	• Completed template listing the reimbursement status of all relevant comparators	Required if filed on or after March 2, 2020	
Pricing and distribution information	• Submitted price per smallest dispensable unit to four decimal places	Required	Required
	• Method of distribution	Required	Required
Budget impact analysis	• Aggregate pan-Canadian budget impact report	Required if filed on or after March 2, 2020	
	• Aggregate pan-Canadian budget impact model		
	• Supporting documentation used in budget impact analysis		

5.1.1 General Information

Application Overview Template

- A completed application overview template.

Signed Cover Letter

- A signed cover letter (an electronic signature is acceptable) from the sponsor, providing the following information:
  - a clear description of the submission or resubmission being filed (e.g., new drug submission filed on a pre-NOC basis)
  - the indication(s) to be reviewed by CADTH
  - the requested reimbursement conditions (if applicable)
  - the names and contact information (email and phone number) for the primary and backup contact(s) that CADTH can contact regarding the submission. The sponsor may designate the consultant(s) preparing the submission as primary and/or backup contact(s). Any changes in contacts should be communicated to CADTH as soon as possible.

Executive Summary

- A high-level summary of the submission or resubmission using the appropriate template (see following). The document must be referenced and must not exceed five pages (excluding references).
  - Executive summary template for a submission
  - Executive summary template for a resubmission

Product Monograph

- Table 11 summarizes the product monograph requirements for submissions or resubmissions.
- Sponsors must immediately notify CADTH, 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 CADTH of any changes to the product monograph could result in temporary suspension of the review.
- Following notification of changes to the product monograph, CADTH will assess the nature and extent of the changes and determine the timelines required for review and, if necessary, incorporate the changes into the review report(s). This could result in the review timelines being delayed, including the submission being considered at a later meeting of the expert review committee or a delay in issuing the final recommendation.
- The sponsor will be apprised of any revisions to the anticipated timeline for the review, deferral by the expert review committee, or the subsequent recommendation not reflecting the most currently available product monograph information relating to the drug under review.

Table 11: Requirements for Filing Product Monograph with CADTH

NOC status	Submission requirements
Pre-NOC	• At the time of filing the submission or resubmission: 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 initially filed with CADTH showing, in tracked changes, all of 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 with CADTH, 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.
Post-NOC	A copy of the most current version of the Health Canada-approved product monograph.

NOC = Notice of Compliance.

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 CADTH template, printed on company letterhead, and signed by an appropriate senior official.
  - Declaration letter template

5.1.2 Health Canada Documentation

Health Canada NOC or NOC/c

Table 12 summarizes the NOC requirements for pre-NOC and post-NOC submissions.

Table 12: Requirements for Filing NOC or NOC/c with CADTH

NOC status	Submission requirements
Pre-NOC	• At the time of filing the submission, a placeholder document indicating the anticipated target date for receipt of an NOC or NOC/c for the indication(s) to be reviewed • A copy of the granted NOC or NOC/c for the indication(s) under review by CADTH, dated and signed by Health Canada, must be sent to CADTH as soon as it is available (i.e., on the day of, or next business day after, receipt from Health Canada) • If the drug receives an NOC/c for the indication(s) being reviewed by CADTH: a copy of the Letter of Undertaking that outlines the confirmatory studies intended to verify the clinical benefit, including an indication of time frames, must also be provided by email to CADTH as soon as it is available
Post-NOC	• A copy of the NOC or NOC/c for the indication(s) for which the drug is to be reviewed by CADTH • If the drug in the submission has received an NOC/c for the indication(s) to be reviewed, the sponsor must provide a copy of the Letter of Undertaking that outlines the confirmatory studies intended to verify the drug's clinical benefit, including an indication of time frames

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

Clarimails or Clarifaxes

Table 13 summarizes the requirements regarding Clarimails/Clarifaxes for pre-NOC and post-NOC submissions.

Table 13: Requirements for Filing Clarimails/Clarifaxes with CADTH

NOC status	Submission requirements
Pre-NOC	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 with CADTH. 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 CADTH with revised summary tables to reflect any additional Clarimails/Clarifaxes as aforementioned.
Post-NOC	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. 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.

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

5.1.3 Efficacy, Effectiveness, and Safety Evidence

Common Technical Document

- A copy of the Common Technical Document sections listed in Table 14 is required.
- 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.

Table 14: Common Technical Document Module Sections

Section	Title
2.5	Clinical Overview
2.7.1	Summary of Biopharmaceutical Studies and Associated Analytical Methods
2.7.3	Summary of Clinical Efficacy
2.7.4	Summary of Clinical Safety
5.2	Tabular Listing of All Clinical Studies

Clinical Studies

- For the clinical studies requirements, CADTH's preference is for any unpublished data to be submitted in manuscript format; however, if unavailable in manuscript format, the information should be provided in accordance with the CONSORT 2010 Statement Checklist, using clearly labelled sections as outlined (i.e., title, abstract, introduction, methods, results, discussion, other information).
- Should an unpublished study submitted as a category 1 requirement (for the "clinical studies" requirements, or listed in the "table of studies" requirement) become published during the review process, sponsor must provide a copy of the published study to CADTH using Collaborative Workspaces.

- Depending on the nature of the information, CADTH will determine the timelines required to review it and incorporate it into the review report(s). This could result in the submission being considered at a later meeting of the expert review committee. The sponsor will be apprised of any revisions to the anticipated timelines for the review.

Standard Reviews

- A reference list and copies of published and unpublished studies that address key clinical issues for the drug under review must be provided. Sponsors must include:
  - copies of any supplemental appendices that are associated with published studies
  - copies of any errata related to any published studies provided. If there are no errata, a placeholder document with a statement confirming this must be provided.
- The first file in the folder must be a reference list of the articles and errata included in the folder.

Tailored Reviews

- A reference list and copies of source documentation for any data that have been included in the completed tailored review template, but not captured in section, 2.5, 2.7.1, 2.7.3, or 2.7.4 of the Common Technical Document, must be provided. Sponsors must include:
  - copies of any errata related to any published studies provided. If there are no errata, a placeholder document with a statement confirming this must be provided
  - if no further source documentation is applicable, a placeholder document with a statement confirming that there is no further applicable source documentation to be provided.
- The first file in the folder must be a reference list of the articles and errata included in the folder.

Resubmission Based on New Clinical Information

- A reference list and copies of all new clinical information that addresses specific issues identified by the expert review committee in the final recommendation document must be provided.
- Include copies of any errata related to any published studies provided, or if there are no errata, a placeholder document with a statement confirming this must be provided.

Clinical Study Reports

For all submissions and resubmissions filed on or after March 2, 2020:

- Complete clinical study reports must be provided for all pivotal studies as well as other studies that address key clinical issues.
- Final or interim clinical study reports must be provided in full and include both the complete study protocol and analysis plan.

Table of Studies

- A tabulated list of all published and unpublished clinical studies using the table of studies template must be provided.
- 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 CADTH's review process must be provided as soon as possible to CADTH using Collaborative Workspaces. CADTH will assess the information upon receiving it and

determine the timelines required to review it and incorporate it into the review report(s). This could result in the submission being considered at a later meeting of the expert review committee. The sponsor will be apprised of any revisions to the anticipated timelines for the review.

Editorials

- A reference list and copies of editorials relating to published clinical studies provided in the submission (i.e., published studies included in the "clinical studies" requirement).
- If no editorials are available, a placeholder document with a statement confirming this must be provided.

New Data

- A reference list and copies of new data generated since the last date that data were reported in the studies included in the Health Canada submission.
- The clinical studies submitted to CADTH are often the same as those submitted to Health Canada, and sometimes these studies are ongoing, with data collected after submission to Health Canada. The data that become available after the study has been submitted to Health Canada are required. These data will be accepted in a variety of formats, including late draft, Clinical Study Report, synopsis, abstract, or conference proceedings.
- If no new data are available, a placeholder document with a statement confirming this must be provided.

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.

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.

5.1.4 Economic Information

Pharmacoeconomic Submission

The pharmacoeconomic submission for all submissions and resubmissions (with the exception of tailored reviews) consists of the following:

- a technical report of the pharmacoeconomic evaluation
- an economic model
- a technical report of the budget impact analysis
- a budget impact model
- any supporting material relevant to the pharmacoeconomic submission.

The technical reports of the pharmacoeconomic evaluation and budget impact analysis 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.

The economic submission (pharmacoeconomic evaluation and electronic model) should be undertaken in accordance with CADTH's *Guidelines for the Economic Evaluation of Health Technologies: Canada (4th edition)*.

Pharmacoeconomic Evaluation: Technical Report

The pharmacoeconomic evaluation must address the following requirements (which are summarized in the checklist provided in Appendix 4):

- The pharmacoeconomic analysis must be in the form of a cost-utility analysis. Only one type of economic evaluation should be submitted. While the submission must be in the form of a cost-utility analysis, life-years should be reported as part of the pharmacoeconomic evaluation.
- 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.
- The base case, and all scenario analyses must be conducted probabilistically.
- The perspective of the publicly funded health care payer must be used in the base case.
- A discount rate of 1.5% for both costs and quality-adjusted life-years (QALYs) must be used in the base case.
- All relevant comparators, including treatments that are currently used off-label in Canadian practice must be included in the base case (and scenario analysis for the reimbursement request). If potentially relevant comparators are excluded from the pharmacoeconomic submission, CADTH may request that the sponsor include these comparators during the review process. CADTH may identify missing comparators during the screening phase and the submission will not be accepted for review. However, in some situations the absence of one or more relevant comparators may not be apparent until the submission has been accepted for review and initiated by CADTH. In these situations, CADTH will notify the sponsor regarding the deficiency and the timelines of the review may be affected (i.e., may result in the submission targeting a later meeting of the expert review committee).
- If more than one comparator is included, results must be reported using a sequential analysis which indicates where the drug lies on the cost-effectiveness efficiency frontier. A suggested reporting format is presented in Appendix 3.
- For submissions in which there are model inputs based on analysis of survival data, the sponsor must provide the Kaplan-Meier curve for each outcome, alongside the parametric distributions tested for model fit.
- Results of the sponsor's base case and scenario analysis for the reimbursement-requested population (if different to 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) and by QALYs (e.g., benefits generated in each health or event state, benefits generated during the trial period versus

the extrapolation period) must be reported based on the probabilistic results. A suggested reporting format is presented in Appendix 3.

- Composite outcomes are generally not satisfactory to inform treatment effect estimates used in a pharmacoeconomic evaluation. Sponsors should base their pharmacoeconomic evaluation on the relevant individual outcomes. If composite outcomes are included in the pharmacoeconomic evaluation, CADTH may request that sponsors include the individual outcomes during the review process. In this situation CADTH will notify the sponsor regarding the deficiency and the timelines of the review may be affected (i.e., may result in the submission targeting a later meeting of the expert review committee).
- 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.
- The specific price(s) submitted to CADTH for the lowest dispensable unit (to four decimal places) must be used in the sponsor's base-case analysis.

Deviations from these requirements must be discussed with and accepted by CADTH in advance of filing the submission. Please submit the following template to requests@cadth.ca with complete details of the deviations from these requirements. Alternative specifications may be considered in scenario analyses.

For additional information on the reporting of results and details of the pharmacoeconomic evaluation, sponsors should refer to the Analysis and Reporting sections of the *Guidelines for the Economic Evaluation of Health Technologies: Canada (4th edition)*, as well as the worked example.

Economic Model

The economic model must address the following requirements:

- An unlocked version of the electronic 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 CADTH in advance if considering alternative program software to ensure that it is acceptable and whether additional requirements will apply.
- The model must be able to function in a standalone environment not requiring access to a web-based platform.
- The sponsor must provide the model in its entirety, meaning CADTH must have full access to the programming code (e.g., macros, VBA code) and be able to fully execute the model based on modifications to parameters of interest. CADTH must be able to vary individual parameters, view the calculations, and run the model to generate results.
- The 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 more than one 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 and report the analysis results sequentially.
- For submissions that use survival data, the sponsor's model must be flexible to easily assess all parametric distributions tested by the sponsor (at minimum, the distributions tested must include: Weibull, Gompertz, Exponential, Log-normal, Log-logistic, Generalized gamma, and Gamma). If any of these distributions are not possible, an acceptable rationale for exclusion must be provided. The sponsor should include one graph that is flexible to present the observed Kaplan-Meier curves and all fitted distribution curves assessed for each treatment and each survival outcome.
- 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 one business day (8 hours) it will be considered by CADTH to be excessive and will not be accepted by CADTH. Run time is determined by CADTH based on CADTH computing powers.

Deviations from these requirements must be discussed with, and accepted by CADTH, in advance of filing the submission. Please submit the following template to requests@cadth.ca with complete details of any proposed deviations from the requirements.

Budget Impact Analysis: Technical Report

The budget impact analysis must address the following requirements (which are summarized in the checklists provided in Appendix 4):

- The base case must reflect a pan-Canadian (national) drug program perspective (excluding Quebec), which should be derived from the following individual drug programs participating in CADTH's drug reimbursement review processes (i.e., British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland and Labrador, and the Non-Insured Health Benefits Program).
- The base case must reflect the complete population identified in the Health Canada-approved indication for which the drug is being submitted to CADTH. If a sponsor is requesting reimbursement for a specific subgroup of the indicated population, or if there are any relevant subgroups, or potential for off-label use, 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 on which the budget impact analysis is based, the review may be suspended until a revised pharmacoeconomic submission reflecting the approved indication is provided.
- When forecasting the budget impact of a new treatment, four years of data must be presented: a one-year baseline period and a three-year forecast period in the base case. The base-case analysis must report costs by year. Discounting should not be applied within the budget impact analysis.
- Results should 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 budget impact analysis. In accordance with the economic evaluation, CADTH may determine that potentially relevant comparators were excluded from the pharmacoeconomic submission.
- The specific price(s) submitted to CADTH for the lowest dispensable unit (to four decimal places) must be used in the sponsor's base case.
- The technical report must incorporate a decision problem, methods, assumptions, and results that align with the submitted budget impact model.

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 budget impact analysis. 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 budget impact analysis (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.
- 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 three 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, etc. if significant) should be considered.

Budget Impact Model

An unlocked version of the electronic budget impact model used in the technical report of the budget impact analysis is a requirement. Additional requirements include:

- The budget impact model must be programmed in Excel.
- The model must be able to function in a standalone environment not requiring access to a web-based platform.
- The sponsor must provide the model in its entirety, meaning CADTH must have full access to the mathematical calculations and be able to fully execute the model based on modifications to parameters of interest.
- The BIA model must be flexible enough to be applied to the context of any of the individual participating drug programs, which may differ with respect to the funding of comparators or the design of the program responsible for drug reimbursement. 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.

- 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.

Deviations from these requirements must be discussed with and accepted by CADTH in advance of filing the submission. Please submit the following template to requests@cadth.ca with complete details of the deviations from these requirements.

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 (as a separate document) 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. In this document, please note the expected model run time.
- The full technical report of the indirect treatment comparison(s) (ITC), if one or more ITC 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 budget impact analysis. This includes but is not limited to utility studies, patient registries, Clinical Study Reports, expert opinion, market research information, epidemiological data on disease incidence and/or prevalence.
  - The technical report(s) must provide details of how input parameter values were derived, including a description of the study or data set, the analysis plan, and results of the analyses. Any modification or transformation of the results to use in the economic model must be described.
- 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.

5.1.5 Epidemiologic Information

Disease Prevalence and Incidence

- Provide the prevalence and incidence of the disease(s) or condition(s) for the indication(s) to be reviewed. Include a breakdown of prevalence by participating province, territory, and First Nations populations (where available).
- References must be provided for this document in the following format:
  - in-text citations numbered in their order of appearance
  - a numbered reference list in the JAMA Oncology format.

Number of Patients Accessing a New Drug

- The following information is required only for a new drug submission or a new combination product submission if one of the components is a new drug (as defined in section 2.1):
  - For the indication(s) to be reviewed by CADTH, the number of patients in Canada currently accessing the new drug to within 20 business days of filing the submission must be provided.
  - This must include the number of patients accessing the drug through each of the different possible mechanisms (such as compassionate use, Health Canada's Special Access Program, and participation in a clinical trial).

- The number of patients accessing the new drug template should be used for providing this information.

5.1.6 Submission Templates for Tailored Reviews

- A completed tailored review submission template.

5.1.7 Reimbursement Status of Comparators

- A completed template summarizing the reimbursement status of all appropriate comparators (for all submissions filed on or after March 2, 2020).

5.1.8 Pricing and Distribution Information

Submitted Price

- The submitted price for the drug, reported to four 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 to CADTH and that must not be exceeded for any of the drug plans following completion of CADTH's review process.
- CADTH does not accept confidential submitted prices for applications filed for review through the drug reimbursement review processes. The submitted price is disclosed in all applicable CADTH reports.
- Only one price (anticipated or current market price) to four decimal places per smallest dispensable unit is to be submitted per drug that is to be reviewed by CADTH (i.e., only one price for all indications undergoing review by CADTH concurrently).
- The submitted price must be used in the pharmacoeconomic evaluation and in the budget impact analysis (BIA) (budget impact reports and the models used to produce the results).
- The price(s) of other treatments included in the pharmacoeconomic evaluation and in the BIA (e.g., comparators, concomitant medications, etc.) are not considered to be confidential and may be disclosed in the CADTH report.

Method of Distribution

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

5.1.9 Implementation Plan for a Cell or Gene Therapy

- A completed a implementation plan template that describes key aspects of their plans for implementing the product in Canada.

5.1.10 Companion Diagnostics

Clinical Utility of Companion Diagnostic

- If applicable, provide a reference list and copies of articles that highlight the clinical utility of the companion diagnostic(s) under review. In this context, clinical utility refers to evidence of improved health outcomes as a result 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.

Price of Companion Diagnostic

- The disclosable price for the companion diagnostic(s) must also be provided.

5.1.11 Additional Letter for Submissions Filed on Pre-NOC Basis

Letter for Sending NOC or NOC/c to CADTH

- Once the NOC or NOC/c has been issued, the sponsor must provide a signed letter, using the Letter for Sending NOC or NOC/c to CADTH template, indicating any wording changes to the Health Canada-approved final product monograph, as compared with the draft product monograph filed in the initial category 1 requirements.
- The letter should be sent to CADTH using Collaborative Workspaces.

5.2 Category 2 Requirements

- CADTH provides secretariat support to the drug plans by ensuring that category 2 requirements have been filed; however, they are not considered as part of the CADTH review or recommendation process.
- The sponsor must also provide the category 2 requirements to all drug plans that require copies (see *Contact Information and Requirements for Drug Plans* for details).
- CADTH does not screen category 2 requirements for completeness. When CADTH notifies a sponsor that category 2 requirements have been received, it does not imply that the provided information meets the requirements of the individual drug plans. If any of the drug plans have questions regarding the filed category 2 requirements, they will contact the sponsors directly.
- Category 2 requirements may be filed concurrently with category 1 requirements (when available). If not provided at the same time as category 1 requirements, one copy of the category 2 requirements must be provided to CADTH using Collaborative Workspaces within 20 business days of the submission or resubmission being accepted for review by CADTH.
- Delayed filing of category 2 requirements will not preclude a review from being placed on the agenda of the targeted expert review committee meeting; however, the embargoed recommendation will not be issued until category 2 requirements are received.

5.2.1 Budget Impact Analyses

The budget impact information provided as part of category 2 requirements should be aligned with the budget impact information provided as part of category 1 requirements (i.e., model design, inputs, assumptions).

Budget Impact Reports

- Budget impact reports for all of the following jurisdictions' drug plans, in accordance with their individual requirements: British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland and Labrador, and the Non-Insured Health Benefits Program. When data specific to Prince Edward Island are unavailable, the BIA for Prince Edward Island is to be based on data from Nova Scotia.
- The base-unit price used in the BIAs must be the same as the price submitted in the category 1 requirements and must be clearly identified in each BIA. Jurisdiction-specific markups or discounts can then be applied, if applicable.

Budget Impact Models

- Copies of the models used to produce the BIAs for all of the following jurisdictions' drug plans, in accordance with their individual requirements: British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland and Labrador, and the Non-Insured Health Benefits Program.

5.2.2 Supporting Documentation Used in Budget Impact Analyses

- A reference list and copies of all supporting documentation used and/or cited in the BIA.
- The reference list must be the first file in the folder of the documents.
- The sponsor is responsible for ensuring that appropriate copyright permissions have been obtained for electronic copies of all supporting documentation included in category 2 requirements of a submission or resubmission, to be shared among the drug plans.

5.2.3 Companion Diagnostics

- If there is a companion diagnostic test associated with the drug, please provide the BIA for drugs and companion diagnostics both in combination and separately, as some jurisdictions fund the two health technologies through separate mechanisms.

5.3 Additional Information

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

5.3.1 Economic Information

During the review period, CADTH may find that the economic evaluation that has been filed by the sponsor contains limitations or 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), CADTH may provide written notice to the sponsor of the limitations identified and provide a description of the specific issues. At this time, the sponsor will be given five business days to notify CADTH which of the following options they would like to pursue:

- The sponsor plans to address the issues raised by CADTH, in which case CADTH will temporarily suspend the review in accordance with section 12.
- The sponsor will not be addressing the limitations raised by CADTH, in which case the review will continue and the limitations will be identified in CADTH's review report.
- The sponsor would like to voluntarily withdraw from the process in accordance with section 13.
- Failure to respond to within five business or a request for an extension will result in temporary suspension of the review in accordance with section 12.

5.3.2 Clinical Study Reports and Periodic Safety Update Reports

CADTH may request complete copies or sections of Clinical Study Reports and Periodic Safety Update Reports from the sponsor. These documents should be provided in searchable electronic format (i.e., PDF or Microsoft Word).

5.3.3 Health Canada Clinical Reviewer Report(s)

- CADTH 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 by CADTH.
- 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 from CADTH, the sponsor should provide the reports to CADTH as soon as available (i.e., on the day of, or the business day after, receipt from Health Canada).

6. Application and Screening Procedure

- An application filed with CADTH for the review of a drug submission or resubmission through the CDR or PPP processes represents a submission or resubmission to all of the participating drug programs.
- By filing a submission or resubmission with CADTH, the sponsor consents to be bound by the terms and conditions specified in the *Procedures for the CADTH Common Drug Review and Interim Plasma Protein Product Review*, including the *CADTH Confidentiality Guidelines for the Common Drug Review and Interim Plasma Protein Product Review* and all provisions regarding withdrawal from the CDR or PPP processes. Consent to the terms and conditions contained herein cannot be revoked by the sponsor at any time during or after or PPP processes.

6.1 Filing a Submission or Resubmission

- The appropriate submission or resubmission requirements filed must adhere to the content, format, and organization stipulated in the current version of the *Procedures CADTH for the Common Drug Review and Interim Plasma Protein Product Review* and any applicable *CADTH Pharmaceutical Reviews Updates*.
- All submission and resubmission requirements must be provided in English.
- Sponsors must be registered with CADTH Collaborative Workspaces before filing a submission or resubmission. For detailed information on how to register please consult CADTH Collaborative Workspaces Registration. Ensure both primary and secondary contacts and any submitting consultants working on an application are registered with Collaborative Workspaces.
- Submissions and resubmissions must be filed using Collaborative Workspaces. To file a submission or resubmission, the sponsor must upload one copy of all category 1 requirements to the corresponding review using Collaborative Workspaces, per the electronic file folder and file format specified in Appendix 5. Submissions and resubmissions must be filed using Collaborative Workspaces during CADTH business hours (between 8:00 a.m. and 4:00 p.m. Eastern time). If filed outside of CADTH business hours, the next business day will be considered the date of transmittal.
- CADTH sends an acknowledgement of receipt to the sponsor as confirmation the submission has been received.
- Sponsors who experience difficulties filing a submission or resubmission using Collaborative Workspaces should contact CADTH by email (requests@cadth.ca) for support or to arrange an alternate delivery method for the submission or resubmission requirements (e.g., by email or mailing a USB flash drive).
- Category 2 requirements may be filed at the same time as category 1 requirements, if available. When not provided at the same time as category 1 requirements, one copy of all category 2 requirements should be submitted to CADTH using Collaborative Workspaces within 20 business days of the submission or resubmission being accepted for review.
- CADTH will provide copies of the category 1 and category 2 requirements to the drug plans to ensure that they have this information before the targeted expert review committee meetings. Sponsors are still required to provide copies of their submission or resubmission — including all drug plan–specific requirements — to the individual drug plans (i.e., CADTH does not provide the category 1 and category 2 requirements on behalf of the sponsor).

6.2 Screening of Submissions and Resubmissions

The following provisions apply to all submissions and resubmissions filed by sponsors or drug plans.

- Applications for submissions and resubmissions are accepted on an ongoing basis.
- Collaborative Workspaces logs the date and time that applications for submissions and resubmissions 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 category 1 requirements.
- Applications are screened in the order they are received.
- If the filed category 1 requirements for a submission or resubmission are deficient or require revision in order to meet the requirements, CADTH sends a notice to the sponsor advising what information needs to be included or revised in order to meet the requirements. Rescreening of category 1 requirements is completed by CADTH as soon as possible after receipt, but may take up to five days.
- Upon receipt of notification of a sponsor's submission or resubmission, the drug plans may identify questions to be addressed in the review process and submit these to CADTH.
- On day 10 of the screening period, CADTH sends a letter to the sponsor advising whether or not the submission or resubmission requirements have been accepted for review.
- Following acceptance for review, the sponsor must also provide the category 1 requirements to all drug plans that require copies (see *Contact Information and Requirements for Drug Plans* for details).

6.2.1 Finalized Information for Submissions Filed on 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 with CADTH (e.g., product monograph). The sponsor must provide all outstanding and/or finalized category 1 requirements to CADTH as soon as they are available.
- CADTH will assess finalized information upon receiving it. Depending on the nature and extent of changes to the information compared with what was originally filed, CADTH will determine the timelines required to review it and incorporate it into the review report(s). This could result in the submission being considered at a later expert review committee meeting. In the event the finalized information is received after the drug has been discussed by the expert review committee, CADTH will review the information and determine if the embargoed recommendation will be issued or if the drug should be placed on the agenda for subsequent meeting of the expert review committee. The sponsor will be apprised of any revisions to the anticipated timelines.
- If additional supporting documentation is required, the sponsor will be apprised of the requirements.
- Once CADTH has notified the sponsor that the finalized category 1 requirements have been accepted, the sponsor must ensure that drug plans are provided with a copy of the finalized category 1 requirements.

6.3 Application Fees for the CADTH Common Drug Review

- All submissions and resubmissions filed by manufacturers are subject to an application fee.
- For details please consult the *Fee Schedule for CADTH Pharmaceutical Reviews*.

6.4 Targeted Time Frames and Tracking

- The key targeted time frames and the status of all reviews are posted on the CADTH website.
- Table 15 indicates the targeted time frames for key tasks within the CADTH's pharmaceutical review processes.
- Depending on the volume or complexity of the material to be reviewed by CADTH, 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.

Table 15: Targeted Timelines for the CDR and PPP Processes

Phase of review	Key milestone	Business days
Standard and tailored reviews		
Screening and administration	Category 1 requirements received by CADTH	0
	Category 1 requirements screened for acceptance	10
	Review initiated	1 to 10
Review of submission or resubmission	Draft review report(s) prepared and sent to sponsor for comments	53
	Sponsor receives draft review report(s) and provides comments	7
	CADTH's responds to comments[a] and final review report(s) prepared	7
Deliberation and recommendation	Brief completed and distributed to the expert review committee and the drug plans	5
	Review of meeting materials by the committee and preparation of discussant reports	10
	Expert review committee meeting	1
	Embargoed recommendation sent to the drug plans and sponsor	8 to 10
Embargo period and options	Embargo period	10 to 30[b]
	Request for clarification or request for reconsideration	Variable[c]
Finalizing and posting	Final recommendation issued to drug plans and sponsor	5
	Final recommendation and review report(s) posted	2
Requests for advice		
Screening and administration	Request for advice received by CADTH	0
	Review approach determined and sponsor invited to provide information	10
	Review initiated	1 to 10
Review of request for advice	Draft review report(s) prepared and sent to manufacturer for comments	≤ 53
	Manufacturer receives draft review report(s) and provides comments	7
	CADTH's responds to comments[a] and final review report(s) prepared	7
Deliberation and recommendation	Brief completed and distributed to the expert review committee and drug plans	5
	Review of meeting materials by the committee and preparation of discussant reports	10
	Expert review committee meeting	1
	Embargoed recommendation sent to drug plans and manufacturer	8 to 10
Embargo period and options	Embargo period	10 to 30[b]
	Request for clarification or request for reconsideration	Variable[c]
Finalizing and posting	Final recommendation issued to drug plans and manufacturer	5
	Final recommendation and review report posted	2

[a] Sponsors will be sent the review team's responses eight business days before the expert review committee meeting.

[b] An extension of up to 20 business days may be requested to prepare a request for reconsideration (i.e., a total of 30 business days).

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

7. Review Procedure

7.1 Ordering and Initiation of Reviews

- All submissions and resubmissions will be assigned to the work schedule on a first-come, first-served basis, as determined by the date the submission or resubmission is accepted for review by CADTH, with the exception of requests for advice, and drug plan-initiated submissions or resubmissions.
- Submissions and resubmissions are typically initiated within 10 business days of acceptance for review. Key dates (including initiation and the targeted expert review committee meeting) are provided only once the submission or resubmission has been accepted for review.
- The timing of when a request for advice will be considered at an expert review committee meeting is based on the nature of the request and the amount of effort required by the review team to address the request. Once completed, requests for advice are generally considered at the earliest available meeting of the expert review committee.
- CADTH posts targeted meeting dates on which submissions and resubmissions may be considered if their reviews are initiated by a given date.
- Before initiating the review of a submission or resubmission, CADTH:
  - provides the sponsor with the name of the contact to whom all inquiries about that submission or resubmission are to be directed
  - establishes a review team, based on the nature of the submission or resubmission, and in consideration of the proposed team members' qualifications, expertise, and compliance with the *CADTH Common Drug Review Conflict of Interest Guidelines*. With the exception of the review manager(s), the names of the review team members are not disclosed to the sponsor
  - determines the appropriate approach for undertaking the review and develops a work plan for the submission or resubmission.

7.2 Reviewing Submissions and Resubmissions

- The following sections outline the process for reviewing standard reviews, tailored reviews, resubmissions, and requests for advice.
- During all reviews, CADTH will determine whether additional information from the sponsor is needed to complete the clinical and/or pharmacoeconomic review. If so, CADTH will contact the sponsor. Delays in providing the requested information may result in a temporary suspension of the review due to incomplete information to conduct a thorough review (see section 12.1).
- If a sponsor submits new information for inclusion in an ongoing review (i.e., after category 1 requirements have been accepted and the review has been initiated), CADTH will determine the timelines required to review the new information and incorporate it into the review reports. This could result in the submission being considered at a later meeting of the expert review committee. The sponsor would be apprised of any revisions to the anticipated timelines for the review.

7.2.1 Standard Reviews

Clinical Review

- The process for standard reviews is outlined in Figure 3.
- At the initiation of the process, CADTH 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)
  - any additional 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, CADTH considers a variety of information, such as clinical practice guidelines, availability of comparator drugs, clinical trial protocols, and stakeholder input (i.e., information from patient groups, clinical experts, drug plans, and expert review committee members). Any clinical end points that were identified by patient groups as being particularly relevant for those living with the condition are highlighted in the protocol document.
- CADTH designs and conducts one or more independent systematic literature searches according to the protocol and to supplement the submission material provided by the sponsor. The search strategy used and the relevant literature that is identified are included in the clinical review. A list of studies that will be included in the systematic review portion of the clinical review is sent to the sponsor for information purposes. Additional relevant evidence from studies that are not included in CADTH's systematic review may be included in other portions of the clinical report. CADTH summarizes and critically appraises 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 group input is summarized in the clinical report and, when discussing the available evidence, CADTH reflects on the input from patient 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 expressed by patients regarding new therapies (including the drug under review). Section 4.1 has additional details on patient engagement in CADTH's review process.
- CADTH review teams typically include at least one clinical expert who provides guidance and interpretation throughout the review. In cases where the drug under review is undergoing or has undergone an expedited review by Health Canada for the indication of interest, CADTH may establish a panel of clinical experts to provide insight into the potential place in therapy. Commentary in the clinical report regarding the potential place in therapy of the drug under review is provided by one or more clinical specialists with expertise in the diagnosis and management of the condition for which the drug is indicated. Section 4.2 has additional details on clinical expert involvement in CADTH's review process.
- The clinical report is prepared in accordance with a template and is finalized in accordance with section 7.3.

Economic Review

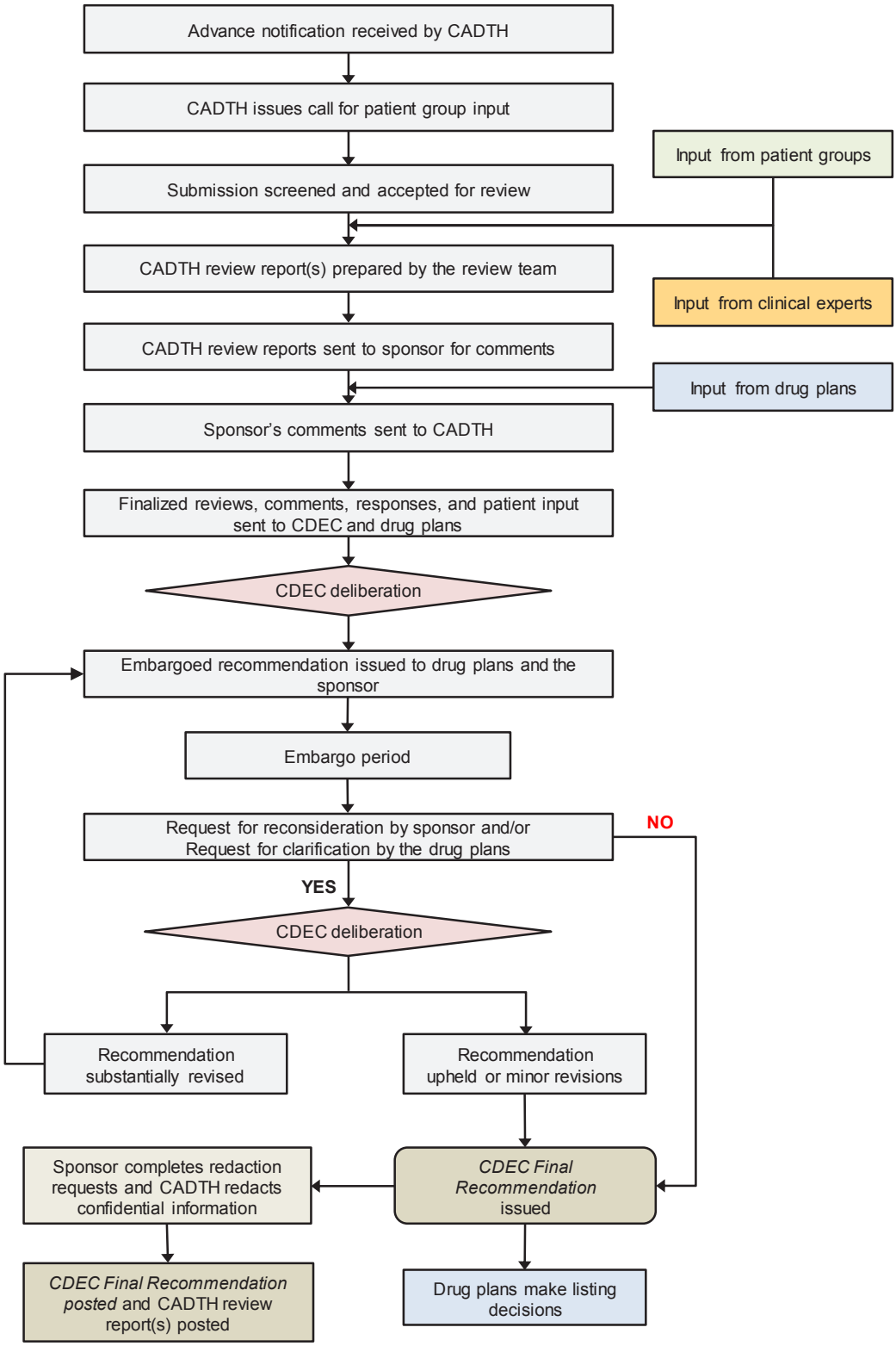
- At the initiation of the process, CADTH economic reviewers work with the clinical reviewers to ensure that clinical information pertinent to the economic review is considered within the clinical review protocol.
- CADTH reviews the sponsor's submitted economic material (i.e., pharmacoeconomic report, economic model, budget impact report, budget impact model, and supporting material), and critically appraises the sponsor's methods, inputs, and assumptions. This part of the appraisal entails:
  - considering the patient input received and whether or how the identified patient information has been incorporated in the economic submission
  - validating the economic model structure, assumptions, and inputs through consultation with the CADTH clinical reviewers and clinical expert(s) involved in the review to ensure the economic model aligns with existing Canadian practice and the findings of the CADTH clinical review
  - testing of the sponsor's submitted economic model to confirm the reproducibility of the probabilistic results and to identify any key drivers of the model results
  - conducting reanalyses to address the limitations noted with the sponsor's economic model to provide revised results (i.e., CADTH base-case reanalysis); if reanalyses are not possible, CADTH will comment on the potential impact of such limitations to the economic findings
  - validating the budget impact model, assumptions, and inputs; reanalyses will be undertaken, as needed, to highlight areas of uncertainty and/or to address limitations noted within the sponsor's budget impact analysis.
- The CADTH economic review report includes a cost comparison table of treatments indicated and/or used for the condition in the Canadian setting.
- CADTH's review of the economic evaluation is conducted in line with CADTH's *Guidelines for the Economic Evaluation of Health Technologies: Canada*.
- The economic report on a drug's cost-effectiveness and budget impact is prepared in accordance with a template and is finalized in accordance with section 7.3.

7.2.2 Tailored Reviews

- The process for tailored reviews is outlined below subsequently and in Figure 3.
- A tailored review consists of the review team conducting an appraisal of the clinical evidence and pharmacoeconomic evaluation filed by the sponsor using a CADTH-provided review template.
- CADTH validates and critically appraises the information provided by the sponsor in the 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.
- CADTH includes its assessment of the submitted information and comments directly into the appropriate sections of the tailored review template. A single report combining both clinical and pharmacoeconomic information is prepared by CADTH for tailored reviews (i.e., *CADTH Clinical and Economic Review Report*).

- Patient group input is summarized in the CADTH report and, when discussing the available evidence, CADTH reflects on the input from patient 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 expressed by patients regarding new therapies (including the drug under review). See section 4.1 for additional details on patient engagement in CADTH's review process.
- CADTH review teams typically include at least one 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 one or more clinical specialists with expertise in the diagnosis and management of the condition for which the drug is indicated. See section 4.2 for additional details on clinical expert involvement in CADTH's review process.
- The *CADTH Clinical and Economic Review Report* for a tailored review is finalized in accordance with section 7.3.

Figure 3: Common Drug Review Process for Standard and Tailored Reviews



CDEC = CADTH Canadian Drug Expert Committee; CDR = CADTH Common Drug Review.

7.2.3 Cell and Gene Therapy Reviews

Clinical Review

The clinical review processes will be completed in accordance with CADTH's standard review procedures as described in section 7.2.1.

Economic Review

The economic review process will be completed in accordance with CADTH's standard review procedures as described in section 7.2.1; however, there will be additional consideration of a pan-Canadian BIA.

Implementation Plan Review

Sponsors will be required to complete a template with key details about their plans to implement the drug in the Canadian system. The drug plans will be asked to review and comment on the completed implementation plan template filed by the sponsor. Their feedback on the implementation plan could help provide early identification of potential access issues within the different jurisdictions, potential issues with administration or distribution mechanisms (e.g., need for specialty clinics) and/or challenges with diagnostic testing requirements. This will approach will allow CADTH and participating jurisdictions to reflect on potential implementation issues and corresponding mitigation strategies in an efficient manner.

Ethics Review

CADTH will identify and describe relevant ethical issues based on published and grey literature. The summary of ethical issues will be incorporated into the draft review reports and the sponsor will have an opportunity to review and provide relevant commentary. The ethics review will provide expert review committee with an overview of ethical considerations to inform their deliberations.

7.2.4 Plasma Protein Product Reviews

The process for the review of plasma protein products is outlined in Figure 4

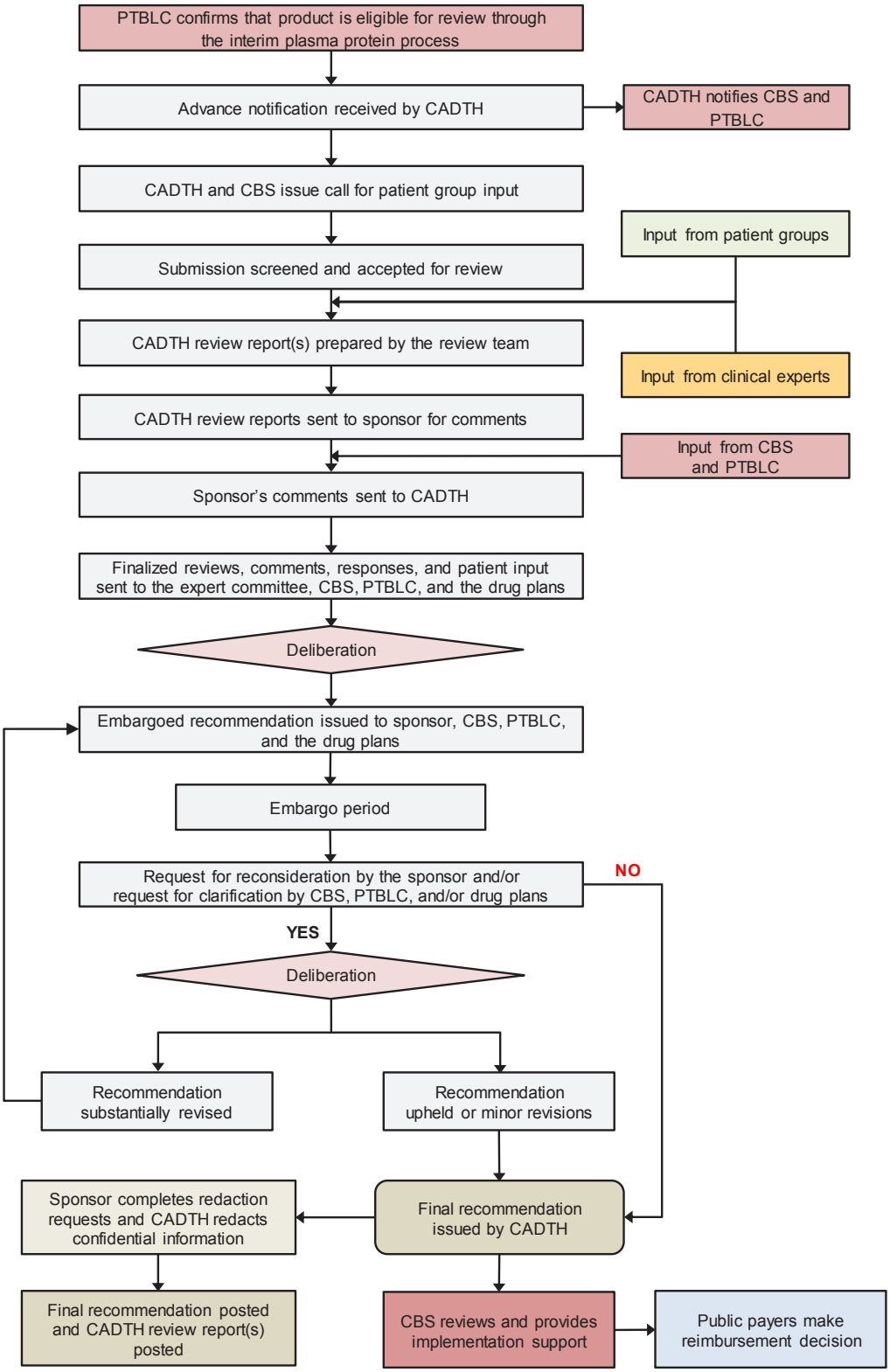
Clinical Review

The clinical review processes will be completed in accordance with CADTH's standard review procedures as described in section 7.2.1.

Economic Review

The economic review process will be completed in accordance with CADTH's standard review procedures as described in section 7.2.1; however, there will be additional consideration of a pan-Canadian BIA.

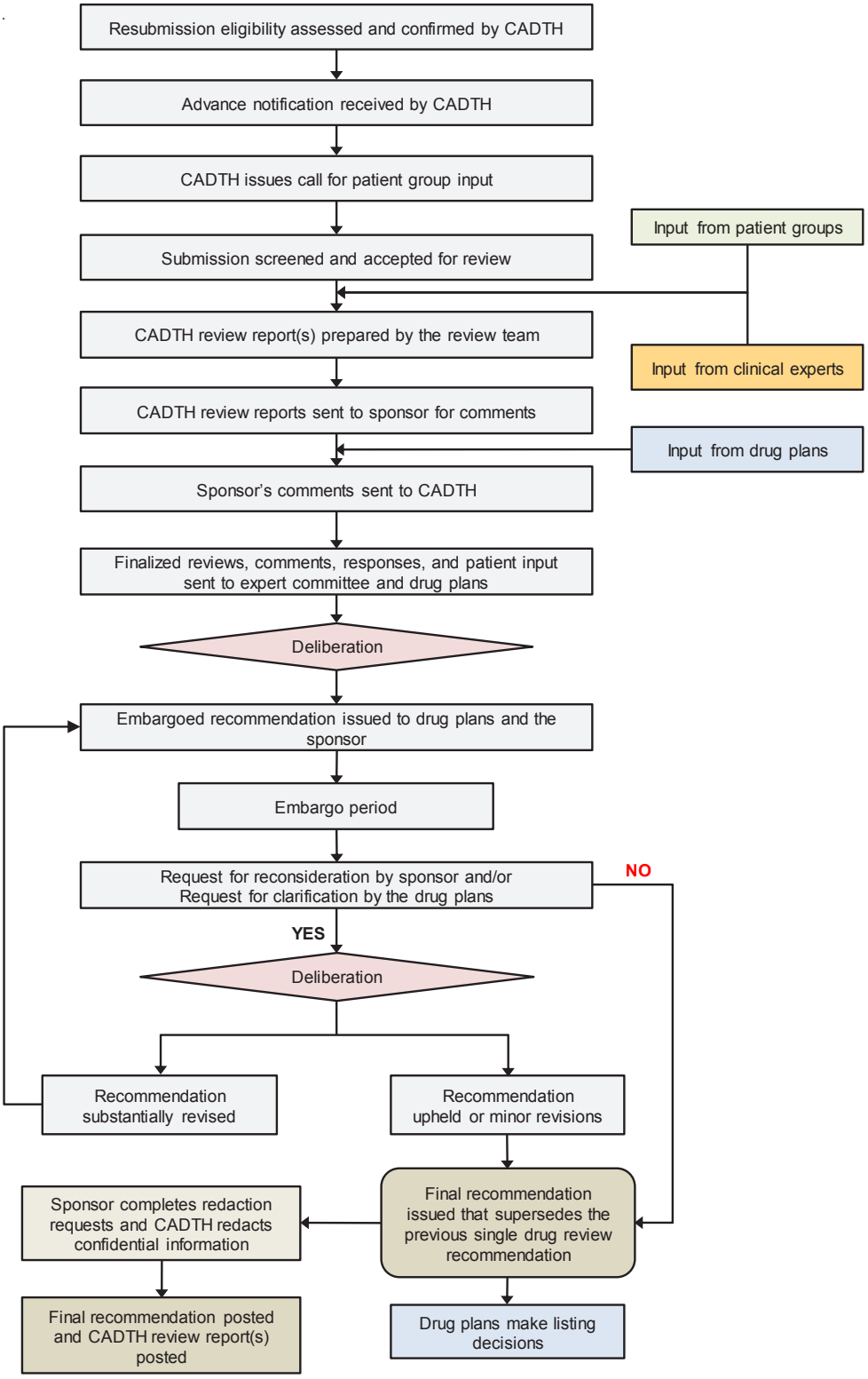
Figure 4: Plasma Protein Product Reviews



7.2.5 Resubmissions

- The process for resubmissions is outlined below and in Figure 5.
- CADTH will determine the length of time required to conduct the review of a resubmission 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 resubmission relative to the target meeting date (e.g., filing earlier in the range provides greater opportunities for CADTH to target an earlier expert review committee meeting)
  - the volume of submissions and resubmissions being reviewed 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 review committee meeting date.
- At the outset of the review of a resubmission, CADTH reviews the information provided by the sponsor and relevant documents from the initial submission and any previous resubmissions. CADTH determines the appropriate approach to assess the new information and determines if a new systematic review is required. In general, the review of a resubmission is conducted in accordance with the procedure used for a standard review (see section 7.2.1).
- The CADTH clinical and/or pharmacoeconomic report(s) for a resubmission are finalized in accordance with section 7.3.

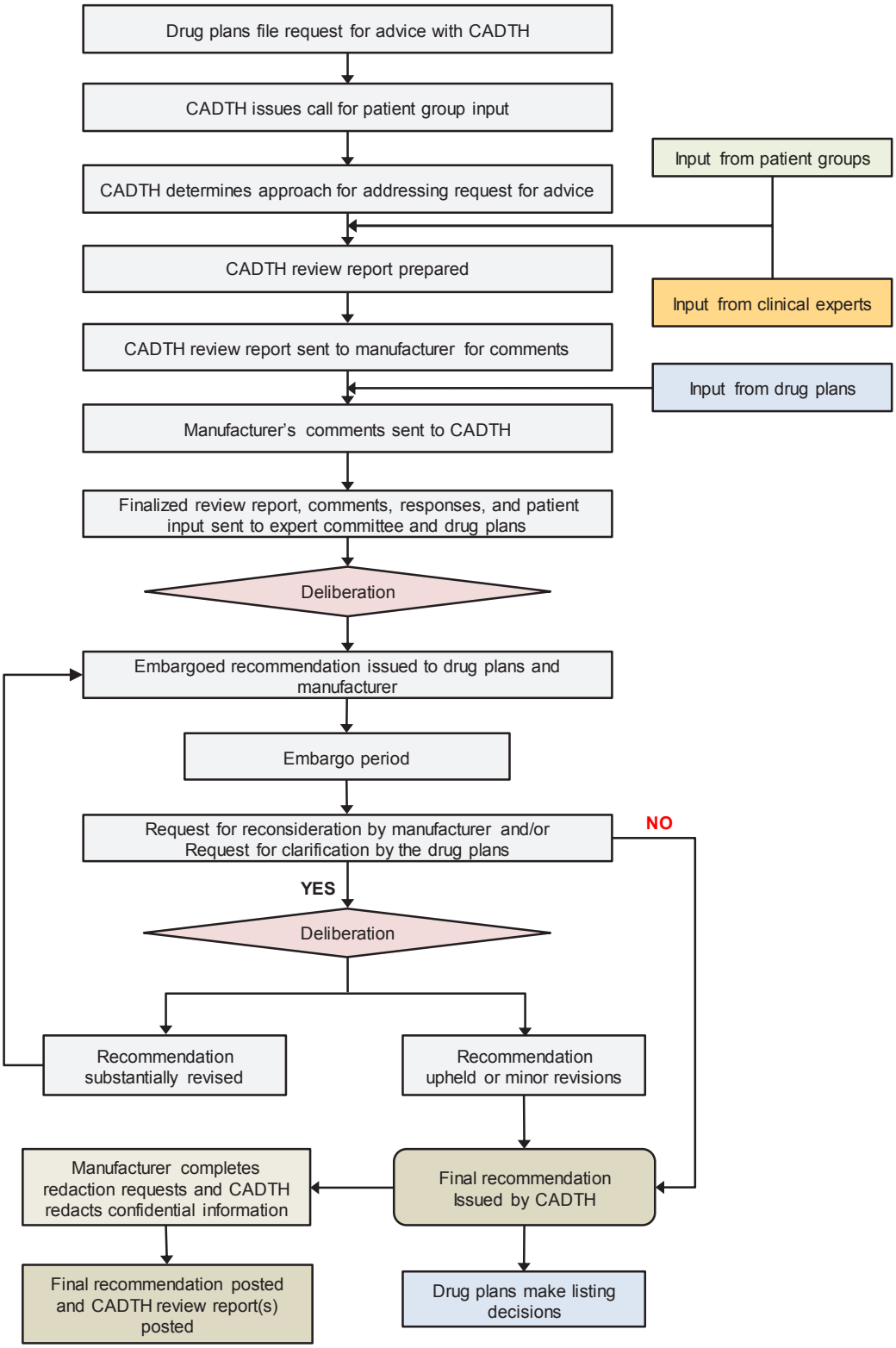
Figure 5: Review Process for Resubmissions



7.2.6 Requests for Advice

- The process for reviewing a request for advice is outlined below and in Figure 6.
- CADTH determines the appropriate approach for responding to the request for advice and develops a work plan for its review within 10 business days of receipt. The date on which CADTH receives a request for advice is considered day zero for the purpose of calculating the time frame for determining the approach for the request. CADTH may seek direction from the members of expert review committees on how to proceed with the request for advice.
- The manufacturer(s) of the drug(s) in question is apprised that a review is being undertaken and the reasons for the review, and is invited to comment or provide information within 10 business days.
- CADTH establishes a review team based on the nature of the request for advice and in consideration of the proposed team members' qualifications, expertise, and compliance with the *CADTH Common Drug Review Conflict of Interest Guidelines*. CADTH will typically include one or more clinical experts on the review team, depending on the nature of the request for advice. With the exception of the review manager(s), the names of the review team members will not be disclosed to the manufacturer.
- CADTH establishes a protocol for the review and may conduct one or more literature searches to identify relevant information. The studies and materials identified through the literature search and any information or data provided by the manufacturer(s) are supplied to the review team to consider as part of the review. Patient group input is summarized and discussed in CADTH's report. See section 4.1 for additional details on patient engagement in CADTH's review process.
- The *CADTH Request for Advice* report is finalized in accordance with section 7.3.

Figure 6: Process for Requests for Advice



7.2.7 Companion Diagnostics

For submissions that include companion diagnostics, CADTH's review process will include the additional considerations noted below.

Clinical Evidence

- As part of the clinical systematic review conducted by CADTH, a subgroup of interest that will be pre-specified in the systematic review protocol will relate to the biomarker status of study participants. This will inform the clinical utility of companion diagnostics by highlighting evidence on the degree to which biomarker testing helps improve outcomes with the corresponding drug treatment.
- CADTH reviewers will also review the sponsor-provided reference list and copies of articles that highlight the clinical utility of the companion diagnostics under review, and may conduct a separate search of the clinical utility of the companion diagnostics. These results will be summarized in an appendix of the clinical review report.

Economic Evidence

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

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.

Clinician Input

- As part of engaging expert clinicians throughout the review process, CADTH may engage additional experts in pathology and/or laboratory testing who would be able to comment on front line clinical aspects of companion diagnostics (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).

Jurisdictional Input

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

7.3 CADTH Review Report(s)

CADTH forwards the draft review report(s) to the sponsor for comments and identification of confidential information, and to the drug plans for their information.

7.3.1 Sponsor Review of Draft Reports

- The sponsor has seven business days following receipt of the draft review report(s) to review and submit written comments about the report(s) to CADTH. This will be the sponsor's only opportunity to provide comments.
- The sponsor's combined comments on the draft review report(s) should not exceed 10 pages in length and must be submitted using the template provided by CADTH. The ten-page limit includes any figures, tables, etc., but does not include the list of references. The formatting of the template (e.g., page margins, table column widths) is not to be altered.
- If the template filed by the sponsor exceeds the ten-page limit, it will not be accepted by CADTH. The sponsor will be asked to re-file their 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 review committee. If CADTH is prevented from achieving the performance metric because of such a delay, sponsors will not be eligible for a partial refund.
- 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 document provided by the sponsor.
- The draft review report(s) are revised by CADTH, as required, based on the sponsor's comments and are included in the committee brief.
- The review team has seven business days to address the comments provided by the sponsor.
- CADTH's responses are sent to the sponsor eight business days before the targeted expert review committee meeting. The responses are provided to the sponsor for information only.
- CADTH's responses are incorporated into the committee brief (see section 8.2) and are shared with drug plans.
- In the case of a submission filed on a pre-NOC basis, CADTH may revise the review report(s) to reflect the final product monograph or other finalized information provided by the sponsor as a result of the NOC or NOC/c being granted.

7.3.2 Identification of Confidential Information

- CADTH will post the review report(s) for all submissions, resubmissions, and requests for advice.
- Sponsors are responsible for identifying and requesting the redaction of any confidential information supplied by the sponsor that was used by CADTH in the preparation of the review report(s) before these documents are posted.
- CADTH forwards the final review report(s) to the sponsor at the same time the final recommendation is issued.

- The sponsor has 10 business days following receipt of the review report(s) to identify confidential information and submit a request for redaction (see Table 16). This will be the sponsor's only opportunity to request redactions from CADTH's review report(s). Sponsors must identify any confidential information in the report(s) by providing:
  - a completed *Identification of Confidential Information Form*
  - a copy of the review report(s) with confidential information highlighted in yellow.
- All requests for redaction must be accompanied by a clearly stated rationale.
- 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.
- CADTH staff will redact confidential information from review report(s) based on the *Identification of Confidential Information Form* completed by the sponsor. Redactions will be made in accordance with the *CADTH Confidentiality Guidelines for the Common Drug Review and Interim Plasma Protein Product Review*.
- The redaction form with CADTH's response will be sent back to the sponsor with a copy of the redacted report(s) for verification by the sponsor.
- The sponsor has five business days to review and confirm the redactions.
- In the case of a disagreement expressed by the sponsor regarding redactions made in the review report(s), CADTH may require additional time to resolve the disagreement in consultation with the sponsor. This additional time could delay publication of the review report(s).
- CADTH may elect to update a previously posted review report should the redacted information become available in the public domain.

Table 16: Time Allotted for Reviewing and Redacting CADTH Review Report(s)

Key milestone	Description and timing	Business days
Sponsor identifies redactions	Sponsors are sent the final review report(s) for identification of confidential information. The sponsor has 10 business days to submit the *Identification of Confidential Information Form* to request redactions to the review report(s).	10
CADTH redactions	CADTH redacts confidential information in accordance with the *CADTH Confidentiality Guidelines for the Common Drug Review and Interim Plasma Protein Product Review*.	8[a]
Sponsor verifies redactions	Sponsors are sent the final redacted and unredacted review report(s) (if applicable) to review and confirm the redactions.	5

[a] Target of eight business days; extensions may be required depending on the nature, complexity, and clarity of the redaction requests.

8. Recommendation Procedure

8.1 Expert Review Committees

- CADTH currently has three drug expert committees that serve as advisory bodies to CADTH. These committees provide drug-related recommendations and advice to the participating public drug programs:
  - CDEC is used for drugs that are reviewed through CADTH's CDR process.
  - CPEC is a subcommittee of CDEC that is used for products that are reviewed through the PPP process.
  - The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) is used for drugs that are reviewed through CADTH's pCODR process.
- The expert committees' recommendations and advice are provided to CADTH to inform the publicly funded drug plans and a range of stakeholders.
- The expert review committees are established in accordance with the following terms of reference:
  - *Canadian Drug Expert Committee Terms of Reference*.
  - *pCODR Expert Review Committee Terms of Reference*
- All expert committee members must comply with the following:
  - *Conflict of Interest Guidelines for CADTH Expert Committee and Panel Members*
  - *Code of Conduct Agreement Form for Members of CADTH Committees and Expert Review Panels*.

8.2 Committee Briefing Materials

- CADTH compiles and distributes the committee brief to all members of the expert review committees and the drug plans 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
    - a summary of the submitted patient group input
    - all patient group input submissions in their entirety
  - CADTH clinical and pharmacoeconomic review report(s)
  - sponsor's comments on CADTH's clinical and pharmacoeconomic review report(s) and the CADTH review team's responses
  - drug plans' listing status for the drug under review and comparators
  - a submission history table of similar drugs reviewed by CADTH
  - additional information
    - reference material (for CADTH's review report[s])
    - a sponsor-provided executive summary and table of studies.

- In addition to the materials in the committee brief, the committee has access to the complete submission or resubmission materials filed by the sponsor.
- CADTH therapeutic review and optimal use reports are included in the committee briefing materials when available and relevant.
- In the case of a request for advice, the CADTH clinical and pharmacoeconomic review report(s) related to the submission or resubmission for which the request for advice is made will be included in the committee brief.

8.3 Expert Review Committee Meetings

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

8.3.1 Preparation for the Expert Review Committee Meeting

- The expert review committee meeting agenda is set by CADTH and the committee chair.
- Three expert review committee members, including one public member, are assigned early in the review process as discussants for each drug under consideration at a scheduled committee meeting. The public member prepares a brief written overview report summarizing the patient group input, and the other two discussants each prepare an overview report summarizing the clinical and pharmacoeconomic evidence. No new clinical or economic information (i.e., information that was not submitted by the sponsor or included by CADTH in the review of the submission or resubmission) is included in the overview reports.
- CADTH staff review the discussant reports to ensure the data are accurate and no new information that was not reviewed in the review report(s) is introduced.
- The final discussant reports are provided to all committee members in advance of the meeting.

8.3.2 Attendees at Expert Review Committee Meetings

- In addition to the expert review committee members, the following people may attend a committee meeting in accordance with the *Canadian Drug Expert Committee Terms of Reference*:
  - 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 CADTH staff and external reviewers contracted by CADTH may actively participate in the presentation of information. The staff role includes provision of administrative and secretariat support. CADTH staff and external reviewers do not have the right to vote.

- External experts (including clinical specialists) attend the expert review committee meetings upon invitation from CADTH. 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.

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

8.3.3 Deliberative Framework and Process

- At the expert review committee meeting, committee members consider and discuss each committee brief on the meeting's agenda in order to make a recommendation.
- Consideration of each submission or resubmission begins with presentations by each of the assigned discussants.
  - The public member makes the first presentation, focusing on 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 other two discussants present their overviews of the clinical and pharmacoeconomic evidence.
- Following the discussant presentations, all expert review committee members provide input, and the review team and invited external experts provide input (as required).
- The key elements supporting the expert review committee's recommendations include the following information available at the time of the review:
  - input from patients and caregivers
  - clinical and economic evidence
  - input from clinical experts
  - existing treatment options (e.g., what is or is not reimbursed and who is covered for reimbursement)
  - the submitted price of the drug under review and the publicly available prices of comparators
  - the sponsor's requested reimbursement conditions (if any) and the evidence supporting those conditions
  - implementation considerations at the jurisdictional level.
- The committee must make a recommendation or defer if additional clarification is needed. If the expert review committee needs additional information from CADTH, the sponsor, or from external experts, the matter will be deferred to a subsequent meeting of the expert review committee, pending the collection of such information. No new information will be allowed at this time. CADTH will determine whether the additional information provided constitutes new information or not.

- Based on the deliberation of the available evidence, expert review committee members choose one of three recommendation options: reimburse, reimburse with conditions, or do not reimburse (see complete details in section 8.4.1), and provide reasons for the recommendation.
- When considering a request for advice, the expert review committee may address the request 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 addressing the request for advice in an updated recommendation document.

In both of the above noted scenarios, an embargoed recommendation will be released as described in section 9.

- The reasons for the recommendation will represent the key considerations and rationale used by the expert review committee in formulating the recommendation. CADTH staff may be tasked with preparing the draft reasons for the recommendation, for approval by the committee.
- The committee members vote on the recommendation in the following manner:
  - only members of the committee may vote
  - all members must vote unless there is a declared conflict of interest that precludes a member from voting
  - the committee members 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.

8.4 Expert Review Committees Recommendation

8.4.1 Recommendation Options

- The expert review committee may recommend one of the following options for a drug under review: that a drug be reimbursed; that a drug be reimbursed with conditions; or that a drug not be reimbursed.
- A description of the recommendation options is provided in Table 17.

Table 17: Description of Recommendations

Reimburse
The drug under review demonstrates comparable or added clinical benefit and acceptable cost/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[b]
Scenarios that could be considered under this category include: • The drug under review demonstrates comparable or added clinical benefit and acceptable cost/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/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/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/cost-effectiveness relative to one or more appropriate comparators[a] is unacceptable, a condition may include a reduced price.
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]

[a] An appropriate comparator is typically a drug reimbursed by one or more drug plans 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. Note: Existing treatment options may include best supportive care and non-pharmaceutical health technologies or procedures.

[b] See section 8.4.2 for additional context regarding potential reimbursement conditions.

8.4.2 Additional Guidance on the Reimburse with Conditions Category

Reimbursement Conditions

- The CADTH drug expert committees 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 18 provides some examples of reimbursement conditions that are commonly included in CADTH recommendations. The examples cited are intended to serve as illustrations only to help guide the reader to better understand some of the factors that CADTH's drug 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.

Table 18: 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 can include: • severity of the condition • patient's 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 can 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 patients who are longer responding and/or benefiting from treatment. Commonly used criteria can include: • need for an invasive intervention (e.g., organ transplantation or ventilation) • initiation of an different therapy for the condition • disease progression.
Prescribing criteria	Provides guidance on the appropriate setting for the treatment. Commonly used criteria can include: • 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 can include: • reduction in price (i.e., cost-effectiveness must be improved). • cost of drug under review not to exceed cost of appropriate comparator(s). • cost of the under review should provide cost savings compared with appropriate comparator(s).

[a] The examples cited in Table 18 are not intended to be an exhaustive list of all possible reimbursement conditions.

Considerations for Significant Unmet Need

- In exceptional cases where there is uncertain clinical and pharmacoeconomic evidence, the CADTH drug 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).
- Please note, the scenario examples noted in Table 19 are intended to serve as illustrations only to help guide the reader to better understand some of the factors that CADTH's drug 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.
- Note: The rarity of the condition will not be the sole consideration for defining significant unmet need. In addition, the condition must be identifiable with reasonable diagnostic precision.

Table 19: 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 with an 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

9. Embargoed Recommendations

In accordance with the *CADTH Confidentiality Guidelines for the Common Drug Review and Interim Plasma Protein Product Review*, stakeholders must maintain the confidentiality of the embargoed recommendation.

9.1 Embargo Period

- The embargo period begins with the issuance of the confidential embargoed recommendation to the sponsor and the drug plans. The intent of the embargo period is to allow time for the sponsor and the drug plans to consider the embargoed recommendation before it is finalized and posted.
- During the embargo period, the following may occur with respect to the embargoed recommendation:
  - Drug plans may submit a request for clarification (section 9.3)
  - Sponsors may make a request for reconsideration (section 9.4).
- The duration of the embargo period is 10 business days; however, sponsors and/or drug plans may request an extension of up to 20 business days (for a total embargo period of 30 business days) for the purposes of preparing and filing a request for reconsideration or request for clarification, respectively.

9.2 Releasing the Embargoed Recommendation

- The confidential embargoed recommendation will be sent to the sponsor and drug plans, along with the final and redacted versions of the CADTH review report(s), eight to 10 business days following the meeting at which the recommendation was made.
- In the case of a submission that was filed on a pre-NOC basis, the embargoed recommendation will not be released until CADTH has received a copy of all required information, including a copy of the NOC or NOC/c. CADTH will review the information and determine if the embargoed recommendation will be issued or if the drug should be placed on a subsequent agenda. The sponsor will be apprised of any revisions to the anticipated timelines.
- The embargoed recommendation will not be released until all category 1 and category 2 requirements for a submission or resubmission have been received by CADTH.
- During the embargoed period, sponsors have 10 business days to review the recommendation and notify CADTH in writing whether or not a request for reconsideration will be made.
- If a request for reconsideration is accepted by CADTH, the final recommendation will not be issued until has considered the request for reconsideration and made a final recommendation.
- The embargoed recommendation is not publicly available. Drug plans and sponsors agree not to act on the embargoed recommendation. All stakeholders must maintain its confidentiality.

9.3 Request for Clarification

- The drug plans may file a request for clarification of an embargoed recommendation within 10 business days of notification of the embargoed recommendation.
- In addition to the standard 10-business day embargo period, the drug programs that participate in the CDR and PPP processes request an extension of up to 20 business days (i.e., a total of 30 business days) for the purpose of preparing and filing a request for reconsideration, in accordance with the following:
  - The request for the extension must be made in writing within 10 business days of receiving the embargoed recommendation.
  - The drug plans must file a request for clarification when an extension is granted.
  - If the drug plans fail to file the request for clarification within the specified time, after requesting an extension to the embargo period, CADTH may issue a final recommendation in accordance with section 10 (typically within five business days).
- A request for clarification is made by filing a written request with CADTH.
- The request for clarification will consist of the reason for the request and a brief description of each point requiring clarification. The request for clarification cannot be based on new information.
- The sponsor and the expert review committee will be notified of the request for clarification.
- The request for clarification is tracked on the CADTH website.
- CADTH will not issue a final recommendation until the drug plans have received a written response to their request for clarification.
- CADTH will prepare a written response to the request for clarification for approval by the committee chair.
- In responding to the request for clarification, CADTH will consult, as required, with the committee chair and the expert review committee, the CADTH review team, and any external expert retained in connection with the submission.
- If, in the judgment of the committee chair and CADTH, the request for clarification requires input and discussion by the full committee complement, it will be placed on the agenda of a subsequent meeting of the expert review committee.
- CADTH will distribute the response to the drug plans, the expert review committee, and the sponsor within five business days of the committee and CADTH determining the response to the request for clarification.
- CADTH will post the details of any requests for clarification that are received during the CDR or PPP review processes. This will include the questions filed by the jurisdictions and the committee's responses to the questions. This information will be included in the final recommendation document. In accordance with the *CADTH Confidentiality Guidelines for the Common Drug Review and Interim Plasma Protein Product Review*, sponsors will have the opportunity to request the redaction of any confidential information before posting on the CADTH website.

9.4 Request for Reconsideration

9.4.1 Sponsor's Request for Reconsideration

- Every sponsor of a drug that is the subject of an embargoed recommendation may file a request for reconsideration of the recommendation during the embargo period.
- A sponsor is entitled to have the embargoed recommendation reconsidered once (this does not include situations where a revised embargoed recommendation has been issued after a request for reconsideration or request for clarification).
- A request for reconsideration can be made only on one or both of the following grounds:
  - the recommendation is not supported by the evidence that had been submitted or the evidence identified in the CADTH review report(s), and/or
  - CADTH and/or the expert review committee failed to act fairly and in accordance with its procedures in conducting the review.
- A request for reconsideration is filed by submitting a written request to CADTH.
  - Requests for reconsideration on the basis that the recommendation is not supported by the evidence that had been submitted or the evidence identified in the CADTH review report(s) must be filed using the reconsideration request template.
  - Any requests for reconsideration on the basis that CADTH and/or the expert review committee failed to act fairly and in accordance with its procedures in conducting the review must be sent to CADTH as a letter that has been signed by a senior company official. Any such requests are addressed on a case-by-case basis.
- If reconsideration is being requested on both of the previously described grounds, sponsors are required to provide both the completed template and a letter that has been signed by a senior company official.
- The request for reconsideration will comprise the reason and grounds for the request, the relief sought, and supporting evidence. A request for reconsideration cannot be made solely because the sponsor disagrees with the recommendation. The request for reconsideration must identify the aspect(s) of the embargoed recommendation with which the sponsor disagrees, and state the grounds for the request for reconsideration.
- No new information will be considered in the reconsideration.
- The sponsor may only file a request for reconsideration during the embargo period.
- In addition to the standard 10-business day embargo period, the sponsor may request an extension of up to 20 business days (i.e., a total of 30 business days) for the purpose of preparing and filing a request for reconsideration, in accordance with the following:
  - The request for the extension must be made in writing within 10 business days of receiving the embargoed recommendation.
  - The sponsor must file a request for reconsideration when an extension is granted.
  - The length of the extension will have an impact on the date of the expert review committee meeting at which the request for reconsideration will be scheduled.
  - If a sponsor fails to file a request for reconsideration within the specified time, after requesting and being granted an extension to the embargo period, CADTH may issue a final recommendation in accordance with section 10 (typically within five business days).
- CADTH notifies the expert review committee and the drug plans of the receipt of the request for reconsideration.

9.4.2 Examination of Request for Reconsideration by CADTH

- CADTH will examine, within five business days, each request for reconsideration to determine whether the issue(s) raised can be resolved in discussions with the sponsor. It may be that the issue(s) can be clarified, and the sponsor will accept the recommendation. It may be that the sponsor has new information, in which case a resubmission is required.
- If CADTH is unable to address the issue(s) raised in the sponsor's request for reconsideration, the request for reconsideration is accepted and will be forwarded to the expert review committee in accordance with section 9.4.4.
- When a request for reconsideration is accepted, the sponsor is offered an optional one-hour teleconference with CADTH to ensure clarity around the key issues raised in the request for reconsideration so that these can be clearly presented by CADTH to the members of the expert review committee (details in section 9.4.3).
- In the event the request for reconsideration is not accepted, CADTH will finalize and issue the recommendation in accordance with section 10. The recommendation will be typically issued five business days after the decision not to accept the request for reconsideration has been communicated to the sponsor.
- CADTH will notify the sponsor of the target date for the expert review committee meeting.
- CADTH considers the following factors when establishing the timelines for reviewing a request for reconsideration:
  - the length of any extensions to the embargoed period granted by CADTH
  - the grounds and complexity of the request for reconsideration
  - the time required by CADTH to examine the grounds for the request and determine whether or not the request will be accepted (e.g., depending on the complexity of the request this can take up to five business days)
  - whether or not the sponsor would like to participate in the one-hour teleconference offered by CADTH to discuss the request for reconsideration
  - the time required to prepare documentation from the reconsideration teleconference for inclusion in the committee brief (e.g., meeting minutes)
  - the deadline for the brief to be delivered to all committee members and the drug plans (i.e., at least 10 business days before the scheduled meeting).

9.4.3 Reconsideration Teleconference

Purpose

- The reconsideration teleconference provides the sponsor an opportunity to elaborate on the issues that were raised in the request for reconsideration that was filed with CADTH.

Attendance

- The sponsor is free to select their attendees; however, CADTH recommends that sponsors ensure that at least one person on the call is familiar with the clinical and economic details of their submission or resubmission and CADTH's review.
- Sponsors are welcome to invite clinical experts to participate in the teleconference, provided they have agreed to maintain the confidentiality of the proceedings, including any CADTH reports and recommendation documents.

- Key CADTH staff will attend the teleconference (e.g., program directors and review team members). The names of the review team members are not disclosed to the sponsor, with the exception of the review manager(s).
- Committee members do not attend the reconsideration teleconference; however, they will be provided with the meeting materials and the summary of the teleconference.

Meeting Agenda

- CADTH will open the meeting by welcoming participants and stating the purpose of the reconsideration teleconference. The remaining content of the meeting and the presenters are at the discretion of the sponsor.
- If providing a presentation, sponsors must limit the number of slides to 30 or fewer.
- To ensure that the teleconference is conducted efficiently, CADTH recommends that the sponsor appoints one of their team members to chair the call. This helps ensure that the sponsor can address all of the key items within the allotted time frame.
- CADTH may pose questions throughout the presentation to help ensure that the issues being raised by the sponsor are clearly understood.

Summary

- The sponsor is required to prepare a draft summary of the discussion using the template provided by CADTH. The summary must not exceed two pages and must be submitted to CADTH in accordance with the deadlines provided at the meeting. Delays in providing the summary could impact the date of the target expert review committee meeting.
- CADTH staff will review and finalize the summary (revising as required to ensure clarity).
- The final summary document will be provided to the sponsor and included in the committee brief.

Teleconference Logistics

- Reconsideration meetings are only offered by teleconference and are a maximum of one hour.
- CADTH will provide the teleconference information before the meeting.
- In-person meetings, video conferencing, or webinars are not offered for reconsideration meetings.
- CADTH may record the reconsideration teleconference for internal purposes.

9.4.4 Expert Committee Reconsideration

- CADTH prepares the committee brief for the request for reconsideration, which includes, but is not limited to the draft recommendation, the request for reconsideration, a summary of CADTH's reconsideration teleconference with the sponsor, and a copy of the original committee brief for the drug that is the subject of the request for reconsideration.
- The reconsideration brief is delivered to all members of the expert committee members and the drug plans at least 10 business days before the scheduled expert committee meeting.
- If the expert committee needs clarification from either the CADTH review team or from the sponsor, or advice from external experts to address the request for reconsideration, the matter will be sent back to CADTH staff to collect such clarification or advice. Consideration of the request for clarification 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 recommendations categories as described in section 8.4 irrespective of the category of recommendation used for the original draft recommendation issued to the drug plans and the sponsor.
- The expert committee will determine if the original recommendation should be upheld or changed.
- Within five business days following the reconsideration, CADTH will issue either a final recommendation or a revised draft recommendation to the sponsor and drug plans.
- CADTH will issue a revised draft recommendation in situations where the committee's recommendation has been substantially revised following a request for reconsideration by a sponsor or a request for clarification by the participating drug plans. Specifically, this process will apply in following circumstances:
  - An initial draft recommendation stating that a drug not be reimbursed was revised by 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.
- CADTH will issue a final recommendation in situations where the initial 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 embargoed recommendation is issued, the options available to the drug plans and sponsor in the additional embargo period will be the same as those currently described in the sections 9.3 and 9.4, respectively.
- The procedure for issuing a final recommendation following a request for reconsideration is described in section 10.

10. Final Recommendations

- After the feedback period has ended, the final recommendation will be issued in the following circumstances:
  - a sponsor does not file a request for reconsideration during the feedback period within the specified time and the drug plans have not filed a request for clarification within the specified time; or the drug plans have filed a request for clarification and written clarification has been provided
  - a sponsor has filed a request for reconsideration and the expert committee has made a recommendation based on the request for reconsideration
  - a sponsor fails to file either a request for reconsideration of the recommendation after requesting and being granted an extension to the embargo period.
- When a final recommendation is issued, CADTH will send a notice of the final recommendation and a copy of the final recommendation to the sponsor and the drug plans.
- All final recommendations are posted on the CADTH website. Sponsors are responsible for identifying and requesting the redaction of any confidential information supplied by the sponsor that has been included in the final recommendation before this document is posted.
- If the sponsor requests that confidential information be redacted from the final recommendation, CADTH will redact the confidential information in accordance with the *CADTH Confidentiality Guidelines for the Common Drug Review and Interim Plasma Protein Product Review*. CADTH will indicate that confidential information was used to make the reimbursement recommendation, and that the sponsor requested that this information be kept confidential, pursuant to the *CADTH Confidentiality Guidelines for the Common Drug Review and Interim Plasma Protein Product Review*.
- Sponsors are asked to identify any confidential information they have supplied in the final recommendation using the identification of confidential information form. All requests for redaction must be accompanied by a clearly stated rationale.
- Sponsors are asked to submit the completed form to CADTH via Collaborative Workspaces by the date and time specified in the notice of the final recommendation (typically 1:00 p.m. Eastern time one business day after the final recommendation was issued).
- Sponsors should only request redactions from the final recommendation and not from the draft recommendation.
- In the case of a disagreement expressed by the sponsor regarding redactions made in the final recommendation, CADTH may require additional time to resolve the disagreement in consultation with the sponsor. This additional time could delay the timeline for posting the final recommendation.

11. Reassessment of Drugs Through the CADTH Therapeutic Review Process

As stated in the *CADTH Therapeutic Review Framework and Process*, one of the outputs from a CADTH therapeutic review may be revised recommendations for drugs that have previously been reviewed through the drug reimbursement reimbursement review processes.

11.1 Identification of Existing CADTH Recommendations

- Existing CADTH recommendations[2] that could be revised as a result of the therapeutic review will be identified and communicated to stakeholders during the scoping phase of the therapeutic review process.
- This could include drugs where existing recommendations have not been issued at the time a CADTH therapeutic review is initiated, but will be reviewed through the drug reimbursement reimbursement review process before the therapeutic review has been completed.

11.2 Patient Input

- Patient engagement opportunities during a therapeutic review are described in detail in the *CADTH Therapeutic Review Framework and Process*.
- Patient engagement at the outset of the therapeutic review will include specific questions related to existing drug reimbursement review recommendations.
- Patient groups will have the opportunity to comment on revisions to existing recommendations that have been proposed by the expert review committee.
- Input from patient groups will be collated by CADTH staff and presented by the public members of the expert review committee, in accordance with the *CADTH Therapeutic Review Framework and Process*.

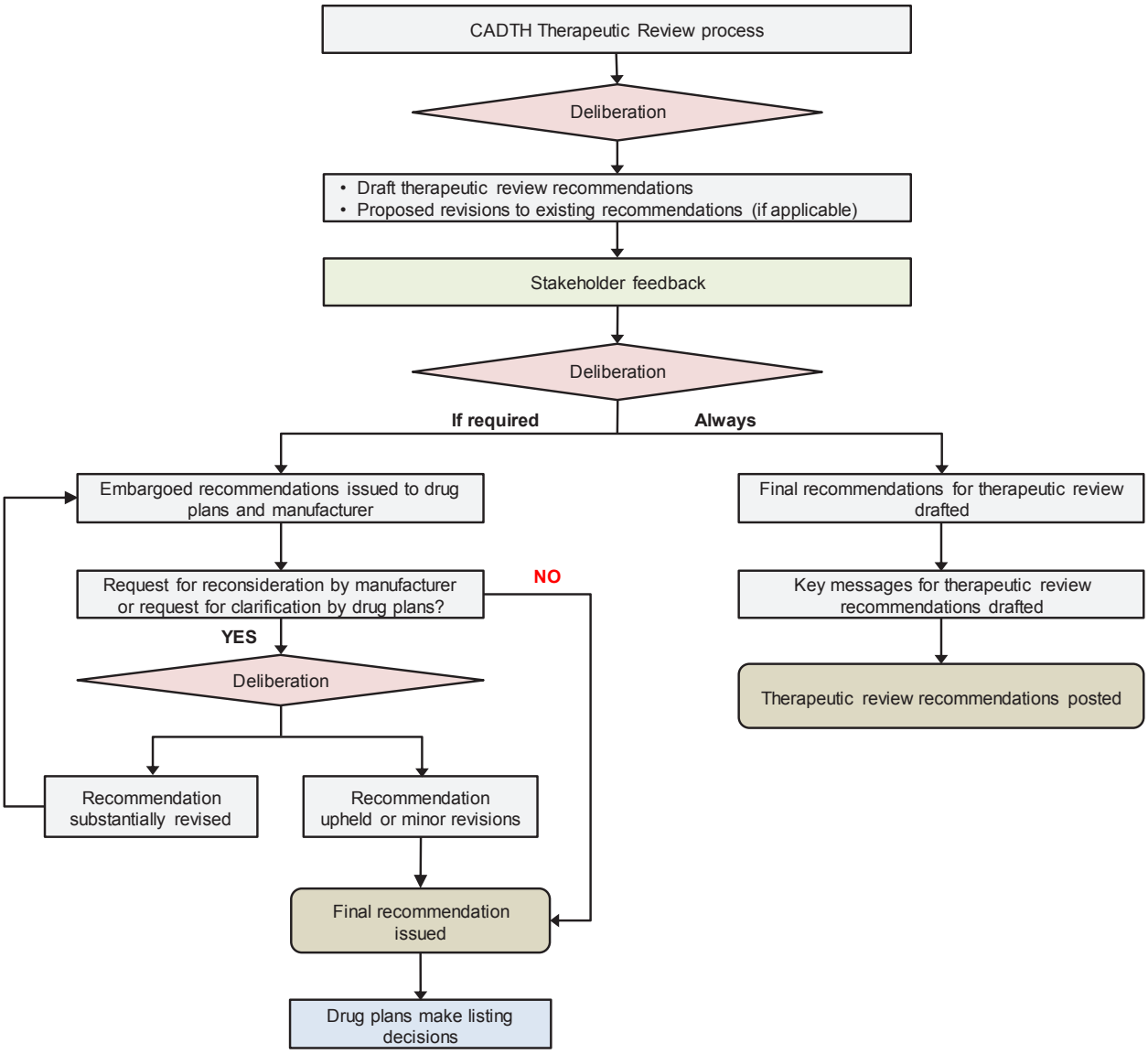
11.3 Expert Committee Recommendation Process

- As part of the deliberative process for therapeutic reviews, the committee will consider whether or not the results of a therapeutic review suggest that any existing recommendations that were issued through the drug reimbursement review process should be revised.
- When considering revisions to existing recommendations, the committee will use the recommendation framework described section 8.4.
- Proposed revisions to existing drug reimbursement review recommendations will be posted for stakeholder feedback at the time the draft therapeutic review recommendations are posted. The following information will be included:
  - the recommendation that may be revised as a result of the therapeutic review
  - the revised reimbursement conditions that are being proposed
  - the rationale for the revision.

[2] The term "review report(s)" in this document refers to the *CADTH Clinical Review Report* and *CADTH Economic Report* typically prepared for a standard review and/or the combined *CADTH Clinical and Economic Review Report* prepared for a tailored review and/or the *CADTH Request for Advice Report* prepared in response to a request for advice. The term "review report(s)" is used as a shortened title to refer to the report(s) collectively or as applicable to a particular type of review.

- Similar to feedback on the draft therapeutic review recommendations, CADTH staff will collate stakeholder feedback on any revisions to existing drug reimbursement review recommendations that have been proposed by the committee. The stakeholder feedback is presented and discussed by the committee.
- Once the therapeutic review recommendations have been finalized, the committee determines if new recommendations should be issued that will supersede any existing recommendations that were issued through the drug reimbursement review processes.
- The committee considers the stakeholder feedback, the evidence from the therapeutic review, and the final therapeutic review recommendations and determines if any existing drug reimbursement review recommendations should be revised. Depending on stakeholder feedback and the final therapeutic review recommendations, this could result in revisions that were not initially identified at the time of stakeholder feedback.
- Manufacturers will be notified by CADTH within 10 business days whether or not a revised drug reimbursement review recommendation will be issued for one or more of its products.
- When the committee has determined that a previous recommendation should be revised, CADTH will issue a new embargoed recommendation in accordance with section 9 (i.e., within eight to 10 business days).
- Manufacturers with one or more products that have received new recommendations will have the opportunity to file a request for reconsideration in accordance with section 9.4.
- Drug plans will have the opportunity to file a request for clarification in accordance with section 9.3.
- CADTH will issue the revised final recommendation in accordance with section 10.
- The revised recommendation will be an abbreviated document noting the following key information:
  - the drug and indication of interest
  - the recommendation, including any conditions (if applicable)
  - a statement indicating that the revised recommendation has been issued as a result of a CADTH therapeutic review
  - a disclaimer indicating that the revised recommendation supersedes the previous drug reimbursement review recommendation for the drug and indication of interest.
- The revised final recommendation will contain no confidential information; therefore, manufacturers will not be asked to complete a redaction request form.
- Posting of the revised final recommendation may occur before posting of the final therapeutic review recommendations.
- A disclaimer will be added to the previous final recommendation stating that it has been superseded by the revised recommendation.

Figure 7: CADTH Therapeutic Review Process for Revising Drug Reimbursement Recommendations



12. Temporary Suspension of a Review

12.1 Suspension Due to Incomplete Information

In the event that CADTH is unable conduct a thorough review and/or an appraisal of a submission or resubmission due to incomplete information, CADTH, in its sole discretion, may temporarily suspend a review in the following manner:

- CADTH may temporarily suspend a review pending receipt and acceptance of all required information.
- CADTH will advise the sponsor in writing that the review has been temporarily suspended. CADTH will indicate the information required in order to re-initiate the review process.
- The CADTH review report(s) will not be sent to the sponsor for comment and the submission or resubmission will not be placed on the agenda for the expert review committee until the review team is satisfied that the sponsor has provided all 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 temporarily suspended at any stage up until the review process has been completed.
- A suspended submission or resubmission is tracked on CADTH's website.

12.2 Suspension Following Notice of Deficiency or Notice of Non-Compliance

- For submissions filed on a pre-NOC basis that receive a notice of deficiency (NOD) or notice of non-compliance (NON) from Health Canada, CADTH will allow the review of certain submissions to be temporarily suspended while resolution of the NOD or NON is discussed with Health Canada.
- In order to be eligible for suspension rather than withdrawal, sponsors must have consented to the information sharing process between CADTH and Health Canada. CADTH 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
- The decision to allow for suspension rather than mandatory withdrawal will be made solely at the discretion of CADTH on a case-by-case basis. If CADTH determines that temporary suspension is not appropriate, the submission will have to be withdrawn in accordance with section 13.1.
- For drugs that undergo temporary suspension as a result of an NOD or NON, the following information would be required in order for CADTH to lift the suspension:
  - A brief summary of the issue and how the sponsor has or is planning to resolve the issue.
  - Any new clinical data filed with Health Canada to address the issue.
  - Advance notification of a minimum of six 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, CADTH 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.

12.3 Suspension for Other Reasons

In the event that questions or issues outside of the regular review process arise (for example, but not limited to, legal issues) regarding the submission or resubmission under review, CADTH, in its sole discretion, may temporarily suspend the review in the following manner:

- CADTH will advise the sponsor in writing that the review has been temporarily suspended. CADTH will indicate the anticipated duration of the suspension period. CADTH also has the discretion to extend the temporary suspension as deemed necessary.
- CADTH's decision to temporarily suspend the review of a submission 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 CADTH, 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 temporarily suspended for reasons outside of the regular review process during any stage of the review process.
- A suspended submission or resubmission is tracked on the CADTH website.

13. Withdrawal From the Process

13.1 Withdrawal Procedure

- A submission or resubmission will be withdrawn from the CDR or PPP processes if:
  - the sponsor voluntarily requests withdrawal of the submission or resubmission
  - Health Canada has withdrawn market authorization
  - Health Canada will not be issuing market authorization
  - CADTH has determined that temporary suspension following the issuance of an NOD or NON is not appropriate
- A sponsor may request voluntary withdrawal from the CDR or PPP processes at any time up until 4:00 p.m. Eastern time three business days before the target committee meeting for the submission, resubmission, or request for advice is scheduled. Voluntary withdrawal will not be permitted after 4:00 p.m. Eastern time three business days before the target committee meeting date.
- In all cases where marketing authorization has been withdrawn or will not be issued by Health Canada, the sponsor must advise CADTH, in writing, as soon as possible.
- All requests for withdrawal from the CDR or PPP processes must be provided in writing and contain the following information:
  - name and signature of the sponsor
  - reason for the withdrawal from the CDR or PPP processes
  - if market authorization was withdrawn, the date on which market authorization was withdrawn.
- CADTH will stop the review immediately upon being notified of the withdrawal or non-issuance of market authorization.
- CADTH will advise the sponsor and drug plans that the review has been withdrawn.
- The CADTH website will be updated to state that the submission or resubmission has withdrawn.
- Sponsors who withdraw from the CDR or PPP processes may be entitled to receive a partial refund of the application fees in accordance with the *Fee Schedule for CADTH Pharmaceutical Reviews*.
- CADTH will retain and/or dispose of copies of the withdrawn submission or resubmission (as described in section 15).

13.2 Re-Filing With CADTH After Withdrawal

- The sponsor is required to re-file a complete submission or resubmission in accordance with section 5.
- The re-filed submission or resubmission must include a list of the changes made as compared with the initial submission or resubmission 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 an NOC or NOC/c, the sponsor is required to file the submission on a post-NOC basis.
- Submissions and resubmissions being re-filed after withdrawal will be screened according to the procedure described in section 6.
- CADTH considers the nature of the submission or resubmission being re-filed and determines the appropriate approach for conducting the review.

14. Implementation Support

14.1 Implementation Panels

Eligibility and Function

- After a final recommendation has been issued, CADTH provides implementation support for the participating jurisdictions and pCPA as required. This support is distinct from CADTH's drug reimbursement review processes and is offered for the purposes of assisting jurisdictions in operationalizing recommendations from CADTH and/or making reimbursement policy decisions.
- At the request of the participating jurisdictions, CADTH may convene panels of clinical experts to assist the jurisdictions in developing and refining reimbursement conditions for certain drug products undergoing negotiation through the pCPA process. These will typically occur after the expert committees have issued a recommendation in favour of reimbursement and provides guidance to CADTH and the jurisdictions that a panel of clinical specialists could be convened to further develop and/or refine the reimbursement conditions proposed in the recommendation. These situations may arise when the committee concludes that the comparative clinical benefit of the drug has been demonstrated, but that a panel of clinical specialists is required in order to specify the conditions that are essential to ensure that the treatment is reimbursed in the most appropriate manner (e.g., by taking into account issues such as budget constraints).
- These panels will only be established at the request of the drug plans that participate in CADTH's drug reimbursement review processes (typically through the FWG).
- The manufacturer of the drug that is the subject of the review by the panel of experts will be notified by CADTH once the process has been initiated and will be included in the process (see below).

Panel Composition

- CADTH will establish a panel consisting of clinical specialists with experience in the diagnosis and management of the condition for which the drug under review is indicated. Whenever possible, CADTH will seek to obtain representation from across Canada. Potential specialists will be identified by CADTH. The number of clinical specialists included on the panels may vary based on input from the participating jurisdictions and the complexity of the drug being considered.
- In accordance with the current policies used by CADTH, the identities of the clinical experts who participate in the panels will remain confidential.
- CADTH will apply its current conflict of interest policy and all panellists will be required to provide completed conflict of interest declarations.
- The attendance at clinical panel meetings will be limited to the clinical specialists, key CADTH staff (i.e., review team members), and representatives from pCPA and/or the participating drug plans. The manufacturer 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 implementation panel meetings.

Patient Engagement

- The clinical panellists will be provided with copies of the patient input submissions that were received in the call for patient input and incorporated into the drug reimbursement review process, as well as the summary of patient input that was prepared by the CADTH review team.
- Similar to the process used in expert committee deliberations, a summary of the patient input will be provided at the outset of the deliberations. This will focus on 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 will provide important context for clinical panel's deliberations.

Implementation Advice Report

- The draft implementation advice report from the panel will be provided to the manufacturer and drug plans for review and comment.
- CADTH will review and discuss the feedback from the manufacturer and drug plans with the expert panel and the guidance report will be revised as required.
- CADTH will prepare responses to the comments which will be provided to the manufacturer at the same time they are issued the final report.
- The final report from this process will be posted on the CADTH website. There will be no confidential information included in the implementation advice report. Manufacturers will not have the opportunity to request any redactions.

14.2 Monitoring Implementation of Recommendations

- CADTH routinely gathers information from the participating drug plans regarding the implementation of recommendations.
- Any issues or challenges are brought forward for discussion with the participating drug programs and pCPA.
- Implementation challenges can often be addressed directly by the jurisdictions and/or pCPA; however, it some situations it may be necessary to obtain additional information and guidance from CADTH. This can include filing a request for advice through the CDR or PPP processes or obtaining decision-making support from CADTH's other services (e.g., Rapid Response or Optimal Use).

15. Document Management

- CADTH's drug reimbursement review processes are complete when all relevant CADTH documents have been posted on the CADTH website (e.g., recommendation, CADTH review report[s], and patient group input).
- CADTH then undertakes the steps detailed in the *CADTH Confidentiality Guidelines for the Common Drug Review and Interim Plasma Protein Product Review* regarding the retrieval, disposal, and archiving of files associated with the review.
- CADTH also follows this document management procedure for a withdrawn submission or resubmission.

CADTH

Appendix 1: Confidentiality Guidelines for the CADTH Common Drug Review and Interim Plasma Protein Product Review

These guidelines must be read in conjunction with the applicable sections of the *Procedures for the CADTH Common Drug Review and Interim Plasma Protein Product Review*, as well as any *CADTH Pharmaceutical Reviews Update* issued after the effective date of the procedure document.

These guidelines are intended to ensure the confidential information obtained for the purposes of the CADTH Common Drug Review (CDR) or Interim Plasma Protein Product Review (PPP) is protected and handled in a consistent manner by CADTH. By filing a submission or resubmission with CADTH, or supplying other information to CADTH for the CDR or PPP processes, a manufacturer or other sponsor consents to these guidelines and agrees to be bound by the terms and conditions herein.

Confidential Information

Sponsor-supplied information that will be treated by CADTH 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 the CDR or PPP processes, but does not include information that:

- is or becomes available to the general public other than as a result 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 Health Technology Assessment 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 section 2 of these guidelines) without restriction as to its use or disclosure.

Confidential information also includes information about a manufacturer's product that is provided to CADTH by Health Canada, with authorization from the manufacturer.

Sponsors must clearly identify any confidential information and provide the rationale for requesting the redaction of any confidential information in accordance with the *Procedures for the CADTH Common Drug Review and Interim Plasma Protein Product Review*.

Handling Confidential Information

1. Responsibilities of CADTH

- CADTH will use reasonable care to prevent the unauthorized use, disclosure, publication, or dissemination of information received by CADTH as part of the CDR or PPP processes that has been designated confidential.
- CADTH will not disclose confidential information in and related to a submission or resubmission to any third party except as permitted by these guidelines, or as required by law or by order of a legally qualified court or tribunal.
- CADTH will use the confidential information solely for the purpose of carrying out its responsibilities with respect to the CDR or PPP processes.

2. Release of Sponsor's Information

CADTH may release any sponsor-supplied information received through the CDR or PPP processes, including confidential information, to the following authorized recipients:

- CADTH staff and review team members (including contractors and clinical experts)
- CADTH expert committee members
- Federal, provincial, and territorial government representatives (including their agencies and departments)
- pan-Canadian Pharmaceutical Alliance office representative(s)
- Canadian Association of Provincial Cancer Agencies (CAPCA) representative(s)
- Canadian Blood Services representative(s)
- members and observers of CADTH's advisory committees and their associated working groups.
- For drugs selected for joint engagement with clinical specialists by CADTH and INESSS, CADTH may release any sponsor-supplied information received through the CDR or PPP processes, including confidential information, to INESSS expert committee members who are participating in meetings with the panel of clinical experts.
- While CADTH 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 CADTH has no control.
- CADTH staff members are required, as a condition of employment, to comply with CADTH's confidentiality requirements, Code of Conduct, and Conflict of Interest Guidelines.
- CADTH does not accept confidential submitted prices for applications filed for review through the CDR or PPP processes. The submitted price is disclosed in all applicable CADTH reports, as well as the recommendation documents posted on the CADTH website.
- The outputs of economic models (e.g., incremental cost-effectiveness ratios) are not considered confidential and will not be redacted.

3. Documents Shared with Authorized Recipients

The documents that CADTH may share with the authorized recipients include, but are not limited to:

- pre-submission-related materials provided by the sponsor
- the sponsor's submission or resubmission
- information provided by the sponsor manufacturer for a drug-plan submission for a request for advice
- redacted and unredacted CADTH review report(s)3
- sponsor's comments about CADTH's review report(s)
- CADTH's responses to the sponsor's comments about draft review report(s)
- draft recommendation
- the redacted and unredacted final recommendation
- the committee brief and reconsideration brief.

[3] The term "review report(s)" in this document refers to the *CADTH Clinical Review Report* and *CADTH Economic Report* typically prepared for a standard review and/or the combined *CADTH Clinical and Economic Review Report* prepared for a tailored review and/or the *CADTH Request for Advice Report* prepared in response to a request for advice. The term "review report(s)" is used as a shortened title to refer to the report(s) collectively or as applicable to a particular type of review.

CADTH provides the following documents to the sponsor (of which the sponsor must maintain confidentiality):

- draft CADTH review report(s)
- CADTH's responses to the sponsor's comments about draft review report(s)
- an draft recommendation
- the final recommendation (until posted on CADTH website)
- a response to request for clarification (if applicable).

The documents that CADTH may post on its website include:

- a tracking document indicating the status of the review, including a submission filed on a pre-NOC basis
- CADTH review report(s) with confidential information redacted
- a final recommendation with confidential information redacted
- a product monograph for the drug under review (typically for the duration of the patient input process).

4. Making Reference to Confidential Information in Public CADTH Documents

CADTH may use confidential information supplied by the sponsor in the preparation of the review report(s) 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 Procedures for the *CADTH Common Drug Review and Interim Plasma Protein Product Review*.

The following principles and provisions will apply to any confidential information that the sponsor has provided and requests to be redacted from the review report(s) or final recommendation:

- CADTH 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 for the CADTH Common Drug Review and Interim Plasma Protein Product Review*.
- CADTH may provide a general description of the type of information that was redacted.
- Submitted prices and the outputs of economic models (e.g., incremental cost-effectiveness ratios) are not considered confidential and will not be redacted.
- In the case of a disagreement expressed by the sponsor regarding redactions made in the review report(s) and/or final recommendation, CADTH 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 CADTH's request to identify confidential information for redaction within three business days, CADTH may proceed with posting the review report(s) and/or final recommendation in accordance with the *Procedures for the CADTH Common Drug Review and Interim Plasma Protein Product Review*.

5. Archiving of Documents Containing Confidential Information

- CADTH 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.
- CADTH will determine at its sole discretion if there is a need to consult this information.
- CADTH staff undertakes regular reviews of archived material. Any material that CADTH determines to be no longer required will be disposed of.

CADTH

Appendix 2: List of Templates

Various hyperlinked templates are provided throughout this document and are to be used when filing a submission or resubmission with CADTH. These templates are also available on the CADTH website.

Pre-Submission Phase Forms

- Pre-submission meeting request form
- Advance notification form
- Tailored review application form
- Resubmission eligibility form
- Submission eligibility form
- Request for deviation from economic requirements form

Templates for Category 1 Requirements

- Application overview template
- Executive summary template for a submission
- Executive summary template for a resubmission
- Table of studies template
- Letter for sending NOC or NOC/c to CADTH
- Declaration letter template
- Number of patients accessing new drugs
- Reimbursement status of comparators template
- Implementation plan for a cell or gene therapy

Templates for Comments, Redactions, and Reconsiderations

- Reconsideration request template
- Sponsor comments template
- Identification of confidential information template

CADTH Submission Templates

- Tailored review submission template

Appendix 3: Suggested Reporting Format for Economics

Table 20: Disaggregated Clinical Outcomes and Costs

Parameter	Drug under review	Comparator #1	Comparator #2 (add as required)
Discounted LYs			
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/event			
Add others (as required)			

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

Table 21: Presentation of Sequential ICURs

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

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

Table 22: Disaggregated Costs in BIA

Parameter	Drug under review	Comparator #1	Comparator #2 (add as required)
Drug program perspective			
Drug acquisition costs			
Premedication costs			
Concomitant medication costs			
Drug costs related to adverse events			
Drug costs related to subsequent treatment			
Dispensing fee			
Mark-up costs			
Total cost			

BIA = budget impact analysis.

Table 23: Presentation of BIA Results

Costs ($)	Year 0 (Baseline year)	Year 1	Year 2	Year 3
Reference scenario				
Drug Under Review	–	–	–	–
Intervention A				
Intervention B				
Total costs				
New drug scenario				
Drug Under Review				
Intervention A				
Intervention B				
Total costs				
Budget impact				
3-year budget impact				

BIA = budget impact analysis.

Appendix 4: Checklists for Preparing Applications

Sponsors may use the checklists used by CADTH, as provided in this appendix, to help ensure that all submission or resubmission requirements for a CADTH Common Drug Review or Interim Plasma Protein Product Review application have been included.

Category 1 requirements	
A.	Standard review filed on a pre-NOC basis
B.	Standard review filed on a post-NOC basis
C.	Cell or gene therapy review filed on a pre-NOC basis
D.	Cell or gene therapy review filed on a post-NOC basis
E.	Plasma Protein Product review filed on a pre-NOC basis
F.	Plasma Protein Product review filed on a post-NOC basis
G.	CADTH–designated tailored review filed on a pre-NOC basis
H.	CADTH–designated tailored review filed on a post-NOC basis
I.	All resubmissions
Category 2 requirements	
J.	All submissions and resubmissions

NOC = Notice of Compliance.

A. Category 1 Requirements for a Standard Review Filed on a Pre-NOC Basis

Requirement	Specific items and criteria	Included
General information		
Application overview	• Completed application overview template	☐
Signed cover letter	• Clear description of submission filed	☐
	• The indication(s) to be reviewed by CADTH	☐
	• Requested reimbursement conditions, if applicable	☐
	• Names and contact information for primary and backup contacts	☐
Executive summary	• Completed executive summary template for a submission	☐
	• Maximum five pages (excluding references)	☐
	• Document is referenced	☐
Product monograph	**At the time of filing:** • A copy of the most recent draft product monograph	☐
	After NOC or NOC/c is issued: • Draft product monograph with tracked clinical and label review changes up to time of Health Canada approval	☐
	• Clean and dated version of Health Canada-approved product monograph	☐
Declaration letter	• Completed declaration letter template	☐
Health Canada documentation		
NOC	**At the time of filing:** • A placeholder document indicating the anticipated NOC date for the indications(s) to be reviewed by CADTH	☐
	After NOC or NOC/c is issued: • Copy of NOC or NOC/c granted for the indication(s) under review • Letter of Undertaking (only if NOC/c granted)	☐ ☐
Clarimails/clarifaxes	**At time of filing:** • Summary table of clinical Clarimails/Clarifaxes up to time of filing	☐
	Ongoing basis until NOC or NOC/c is issued: • Revised clinical Clarimail/Clarifax summary table(s)	☐
Efficacy, effectiveness, and safety Information		
Common technical document	• Section 2.5	☐
	• Section 2.7.1	☐
	• Section 2.7.3	☐
	• Section 2.7.4	☐
	• Section 5.2	☐
	• Or a statement indicating section(s) were not required by Health Canada	☐
Clinical studies and errata	• Reference list of key clinical issues 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)	☐ ☐

Requirement	Specific items and criteria	Included
Clinical study reports	• Complete clinical study reports for all pivotal studies as well as other studies that address key clinical issues (if submission is filed on or after March 2, 2020)	☐
Table of studies	• Completed table of studies template	☐
Editorials	• Reference list of editorial articles (or document stating none found)	☐
	• Copies of editorial articles	☐
New data	• Reference list of new data (or statement that none available)	☐
	• Copies of new data available	☐
	• Reference list (or statement that none available)	☐
Validity of outcome measures	• Copies of validity of outcome measure references available	☐
Indirect comparison	• Copies of any indirect comparisons used in pharmacoeconomic evaluation	☐
	• Indirect comparison technical report	☐
Economic information		
Pharmacoeconomic evaluation: Technical report	• Pharmacoeconomic evaluation for the full population identified in the indication(s) to be reviewed by CADTH	☐
	• Scenario analysis of the population identified in the reimbursement request (if different from the population in the full indication)	☐
	• Economic evaluation is a cost-utility analysis	☐
	• Base case reflects the public health care payer perspective	☐
	• 1.5% discount rate on costs and QALYs	☐
	• All relevant comparators have been included	☐
	• Submitted price per smallest dispensable unit used	☐
	• All results are presented probabilistically	
	• All ICERs reported sequentially if more than one comparator is presented	☐
	• Results are presented in disaggregated format	☐
	• Treatment effect measures should generally not use composite endpoints	☐
	• If relevant, a graph with Kaplan-Meier curve and parametric distributions for each relevant outcome	☐
	• If relevant, companion diagnostic test information incorporated	☐
	• Alignment between the pharmacoeconomic evaluation technical report and the economic model	☐
Economic model	• Model is programmed in Excel	☐
	• Model is fully unlocked and executable, and all code is provided	☐
	• Model functions in a standalone environment and does not require access to a web-based platform	☐
	• Probabilistic analyses runs without error	☐
	• Results of the probabilistic analysis are stable (congruence test provided)	☐
	• Where there are multiple comparators, the model runs treatments simultaneously and results of all comparators are presented	☐

Requirement	Specific items and criteria	Included
Supporting documentation	• Model user guide	☐
	• Indirect comparison technical report	☐
	• Unpublished studies or analyses used in the pharmacoeconomic evaluation	☐
	• Document summarizing key sources of information for the companion diagnostic test	☐
Budget impact analysis		
Budget impact analysis: technical report	• Base case reflects pan-Canadian (national) perspective (excluding Quebec)	☐
	• Base case reflects the Health Canada-approved (proposed) indication	☐
	• Scenario analysis of the reimbursement request population (if different from the Health Canada-approved (proposed) indication)	☐
	• Base-case analysis uses a four-year time horizon (including the 12 months before the public funding of the drug under review for the indication being evaluated)	☐
	• Analyses presented deterministically	☐
	• All relevant comparators included	☐
	• Submitted price per smallest dispensable unit used	☐
	• Report includes at minimum decision problem, methods, assumptions and results	☐
Budget impact model	• Model is programmed in Excel	☐
	• Model is fully unlocked and executable, and all code is provided.	☐
	• Model functions in a standalone environment and does not require access to a web-based platform	☐
	• Model is flexible and allows assessment for each individual drug program	☐
	• Input values specific to the individual drug program	☐
	• Breakdown of costs by perspective reported within the submitted model	☐
	• Alignment between the technical report and the model	☐
Supporting documentation	• Reference list of all supporting documentation used and/or cited in BIAs	☐
	• Unpublished studies or analyses used to inform the budget impact analysis	☐
Epidemiologic information		
Disease prevalence and incidence	• Disease prevalence and incidence with specified breakdown (if available)	☐
	• Document is referenced	☐
Number of patients accessing a new drug	• Number of patients accessing the new drug up to within 20 business days of filing the submission (Note: this requirement is only for a new drug submission or a new combination product submission if one of the components is a new drug.) • Use the Number of Patients Accessing New Drug template	☐
Reimbursement status of comparators	• A completed template summarizing the reimbursement status of all appropriate comparators (for all submissions filed on or after March 2, 2020).	☐
Pricing and distribution information		
Price and distribution method	• Submitted unit pricing to four decimal places	☐
	• Method of distribution	☐

Requirement	Specific items and criteria	Included
Companion diagnostic(s)		
Companion diagnostics	• Reference list	☐
	• Articles that highlight the clinical utility of the companion diagnostic(s)	☐
	• Disclosable price for the companion diagnostic(s)	☐
Additional letter for submissions filed on Pre-NOC basis		
Letter for sending NOC or NOC/c to CADTH	**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)	☐

ICER = incremental cost-effectiveness ratio; NOC = Notice of Compliance; NOC/c = Notice of Compliance with conditions.

B. Category 1 Requirements for a Standard Review Filed on a Post-NOC Basis

Requirement	Specific items and criteria	Included
General information		
Application overview	• Completed application overview template	☐
Signed cover letter	• Clear description of submission filed	☐
	• The indication(s) to be reviewed by CADTH	☐
	• Requested reimbursement conditions, if applicable	☐
	• Names and contact information for primary and backup contacts	☐
Executive summary	• Completed executive summary template for a submission	☐
	• Maximum five pages (excluding references)	☐
	• Document is referenced	☐
Product monograph	• A copy of the most current version of the Health Canada-approved product monograph	☐
Declaration letter	• Completed declaration letter template	☐
Health Canada documentation		
NOC	• A copy of the NOC or NOC/c granted for the indication(s) to be reviewed	☐
	• Letter of Undertaking (only if NOC/c granted)	☐
Clarimails/clarifaxes	• Summary table of any clinical Clarimails/Clarifaxes up to the time of NOC or NOC/c being issued	☐
Efficacy, effectiveness, and safety information		
Common technical document	• Section 2.5	☐
	• Section 2.7.1	☐
	• 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 of key clinical issues 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	• Complete clinical study reports for all pivotal studies as well as other studies that address key clinical issues (if submission is filed on or after March 2, 2020)	☐
Table of studies	• Completed table of studies template	☐
Editorials	• Reference list of editorial articles (or a document stating none found)	☐
	• Copies of editorial articles	☐
New data	• Reference list of new data (or statement that none available)	☐
	• Copies of new data available	☐
Validity of outcome, measures	• Reference list (or statement that none available)	☐
	• Copies of validity of outcome measure references available	☐
Indirect comparison	• Copies of any indirect comparisons used in pharmacoeconomic evaluation	☐
	• Technical report	☐

Requirement	Specific items and criteria	Included
Economic information		
Pharmacoeconomic evaluation: Technical report	• Pharmacoeconomic evaluation for the full population identified in the indication(s) to be reviewed by CADTH	☐
	• Scenario analysis of the population identified in the reimbursement request (if different from the population in the full indication)	☐
	• Economic evaluation is a cost-utility analysis	☐
	• Base case reflects the public health care payer perspective	☐
	• 1.5% discount rate on costs and QALYs	☐
	• All results are presented probabilistically	☐
	• Submitted price per smallest dispensable unit used	☐
	• All ICERs reported sequentially if more than one comparator is presented	☐
	• Results are presented in disaggregated format	☐
	• Treatment effect measures should generally not use composite endpoints	☐
	• If relevant, a graph with Kaplan-Meier curve and parametric distributions for each relevant outcome	☐
	• If relevant, companion diagnostic test information incorporated	☐
	• Alignment between the pharmacoeconomic evaluation technical report and the economic model	☐
Economic model	• Model is programmed in Excel	☐
	• Model is fully unlocked and executable, and all code is provided	☐
	• Model functions in a standalone environment and does not require access to a web-based platform	☐
	• Probabilistic analyses runs without error	☐
	• Results of the probabilistic analysis are stable (congruence test provided)	☐
	• Where there are multiple comparators, the model runs treatments simultaneously and results of all comparators are presented	☐
Supporting documentation	• Model user guide	☐
	• Indirect comparison technical report	☐
	• Unpublished studies or analyses used in the pharmacoeconomic evaluation	☐
	• Document summarizing key sources of information for the companion diagnostic test	☐
Budget impact analysis		
Budget impact analysis: technical report	• Base case reflects pan-Canadian (national) perspective (excluding Quebec)	☐
	• Base case reflects the Health Canada-approved indication	☐
	• Scenario analysis of the reimbursement request population (if different from the Health Canada-approved indication)	☐
	• Base-case analysis uses a four-year time horizon (including the 12 months before the public funding of the drug under review for the indication being evaluated)	☐
	• Analyses presented deterministically	☐
	• All relevant comparators included	☐
	• Submitted price per smallest dispensable unit used	☐
	• Report includes at minimum decision problem, methods, assumptions and results	☐

Requirement	Specific items and criteria	Included
Budget impact model	• Model is programmed in Excel	☐
	• Model is fully unlocked and executable, and all code is provided.	☐
	• Model functions in a standalone environment and does not require access to a web-based platform	☐
	• Model is flexible and allows assessment for each individual drug program	☐
	• Input values specific to the individual drug program	☐
	• Breakdown of costs by perspective reported within the submitted model	☐
	• Alignment between the technical report and the model	☐
Supporting documentation	• Reference list of all supporting documentation used and/or cited in BIAs	☐
	• Unpublished studies or analyses used to inform the budget impact analysis	☐
Epidemiologic information		
Disease prevalence and incidence	• Disease prevalence and incidence with specified breakdown (if available)	☐
	• Document is referenced	☐
Number of patients accessing a new drug	• Number of patients accessing the new drug up to within 20 business days of filing the submission (Note: this requirement is only for a new drug submission or a new combination product submission if one of the components is a new drug.) • Use the Number of Patients Accessing New Drug template	☐
Reimbursement status of comparators	• A completed template summarizing the reimbursement status of all appropriate comparators (for all submissions filed on or after March 2, 2020).	☐
Pricing and distribution information		
Price and distribution method	• Submitted unit pricing to four decimal places	☐
	• Method of distribution	☐
Companion diagnostic(s)		
Companion diagnostics	• Reference list	☐
	• Copies of articles that highlight the clinical utility of the companion diagnostic(s)	☐
	• Disclosable price for the companion diagnostic(s)	☐

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

C. Category 1 Requirements for a Cell or Gene Therapy Filed on a Pre-NOC Basis

Requirement	Specific items and criteria	Included
General information		
Application overview	• Completed application overview template	☐
Signed cover letter	• Clear description of submission filed	☐
	• The indication(s) to be reviewed by CADTH	☐
	• Requested reimbursement conditions, if applicable	☐
	• Names and contact information for primary and backup contacts	☐
Executive summary	• Completed executive summary template for a submission	☐
	• Maximum five pages (excluding references)	☐
	• Document is referenced	☐
Product monograph	**At the time of filing:** • A copy of the most recent draft product monograph	☐
	After NOC or NOC/c is issued: • Draft product monograph with tracked clinical and label review changes up to time of Health Canada approval	☐
	• Clean and dated version of Health Canada-approved product monograph	☐
Declaration letter	• Completed declaration letter template	☐
Health Canada documentation		
NOC	**At the time of filing:** • A placeholder document indicating the anticipated NOC date for the indications(s) to be reviewed by CADTH	☐
	After NOC or NOC/c is issued: • Copy of NOC or NOC/c granted for the indication(s) under review	☐
	• Letter of Undertaking (only if NOC/c granted)	☐
Clarimails/clarifaxes	**At time of filing:** • Summary table of clinical Clarimails/Clarifaxes up to time of filing	☐
	Ongoing basis until NOC or NOC/c is issued: • Revised clinical Clarimail/Clarifax summary table(s)	☐
Efficacy, effectiveness, and safety Information		
Common technical document	• Section 2.5	☐
	• Section 2.7.1	☐
	• 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 of key clinical studies and any errata	☐
	• Copies of studies addressing key clinical issues	☐
	• Copies of any errata (or a document stating that none found)	☐
Clinical study reports	• Complete clinical study reports for all pivotal studies as well as other studies that address key clinical issues (if submission is filed on or after March 2, 2020)	☐

Requirement	Specific items and criteria	Included
Table of studies	• Completed table of studies template	☐
Editorials	• Reference list of editorial articles (or document stating none found)	☐
	• Copies of editorial articles	☐
New data	• Reference list of new data (or statement that none available)	☐
	• Copies of new data available	☐
Validity of outcome measures	• Reference list (or statement that none available)	☐
	• Copies of validity of outcome measure references available	☐
Indirect comparison	• Copies of any indirect comparisons used in pharmacoeconomic evaluation	☐
	• Technical report	☐
Economic information		
Pharmacoeconomic evaluation: Technical report	• Pharmacoeconomic evaluation for the full population identified in the indication(s) to be reviewed by CADTH	☐
	• Scenario analysis of the population identified in the reimbursement request (if different from the population in the full indication)	☐
	• Economic evaluation is a cost-utility analysis	☐
	• Base case reflects the public health care payer perspective	☐
	• 1.5% discount rate on costs and QALYs	☐
	• All results are presented probabilistically	☐
	• Submitted price per smallest dispensable unit used	☐
	• All ICERs reported sequentially if more than one comparator is presented	☐
	• Results are presented in disaggregated format	☐
	• Treatment effect measures should generally not use composite endpoints	☐
	• If relevant, a graph with Kaplan-Meier curve and parametric distributions for each relevant outcome	☐
	• If relevant, companion diagnostic test information incorporated	☐
	• Alignment between the pharmacoeconomic evaluation technical report and the economic model	☐
Economic model	• Model is programmed in Excel	☐
	• Model is fully unlocked and executable, and all code is provided	☐
	• Model functions in a standalone environment and does not require access to a web-based platform	☐
	• Probabilistic analyses runs without error	☐
	• Results of the probabilistic analysis are stable (congruence test provided)	☐
	• Where there are multiple comparators, the model runs treatments simultaneously and results of all comparators are presented	☐
Supporting documentation	• Model user guide	☐
	• Indirect comparison technical report	☐
	• Unpublished studies or analyses used in the pharmacoeconomic evaluation	☐
	• Document summarizing key sources of information for the companion diagnostic test	☐

Requirement	Specific items and criteria	Included
Budget impact analysis		
Budget impact analysis: technical report	• Base case reflects pan-Canadian (national) perspective (excluding Quebec)	☐
	• Base case reflects the Health Canada-approved (proposed) indication	☐
	• Scenario analysis of the reimbursement request population (if different from the Health Canada-approved (proposed) indication)	☐
	• Base-case analysis uses a four-year time horizon (including the 12 months before the public funding of the drug under review for the indication being evaluated)	☐
	• Analyses presented deterministically	☐
	• All relevant comparators included	☐
	• Submitted price per smallest dispensable unit used	☐
	• Report includes at minimum decision problem, methods, assumptions and results	☐
Budget impact model	• Model is programmed in Excel	☐
	• Model is fully unlocked and executable, and all code is provided	☐
	• Model functions in a standalone environment and does not require access to a web-based platform	☐
	• Model is flexible and allows assessment for each individual drug program	☐
	• Input values specific to the individual drug program	☐
	• Breakdown of costs by perspective reported within the submitted model	☐
	• Alignment between the technical report and the model	☐
Supporting documentation	• Reference list of all supporting documentation used and/or cited in BIAs	☐
	• Unpublished studies or analyses used to inform the budget impact analysis	☐
Reimbursement status of comparators	• A completed template summarizing the reimbursement status of all appropriate comparators (for all submissions filed on or after March 2, 2020).	☐
Epidemiologic information		
Disease prevalence and incidence	• Disease prevalence and incidence with specified breakdown (if available)	☐
	• Document is referenced	☐
Pricing and distribution information		
Price and distribution method	• Submitted unit pricing to four decimal places	☐
	• Method of distribution	☐
Implementation plan	• Completed implementation plan template	☐
Companion diagnostic(s)		
Companion diagnostics	• Reference list	☐
	• Copies of articles that highlight the clinical utility of the companion diagnostic(s)	☐
	• Disclosable price for the companion diagnostic(s)	☐
Additional letter for submissions filed on Pre-NOC basis		
Letter for sending NOC or NOC/c to CADTH	**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)	☐

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

D. Category 1 Requirements for a Cell or Gene Therapy Filed on a Post-NOC Basis

Requirement	Specific items and criteria	Included
General information		
Application overview	• Completed application overview template	☐
Signed cover letter	• Clear description of submission filed	☐
	• The indication(s) to be reviewed by CADTH	☐
	• Requested reimbursement conditions, if applicable	☐
	• Names and contact information for primary and backup contacts	☐
Executive summary	• Completed executive summary template for a submission	☐
	• Maximum five pages (excluding references)	☐
	• Document is referenced	☐
Product monograph	• A copy of the most current version of the Health Canada-approved product monograph	☐
Declaration letter	• Completed declaration letter template	☐
Health Canada documentation		
NOC	• A copy of the NOC or NOC/c granted for the indication(s) to be reviewed	☐
	• Letter of Undertaking (only if NOC/c granted)	☐
Clarimails/clarifaxes	• Summary table of any clinical Clarimails/Clarifaxes up to the time of NOC or NOC/c being issued	☐
Efficacy, effectiveness, and safety information		
Common technical document	• Section 2.5	☐
	• Section 2.7.1	☐
	• 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 of key clinical issues 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	• Complete clinical study reports for all pivotal studies as well as other studies that address key clinical issues (if submission is filed on or after March 2, 2020)	☐
Table of studies	• Completed table of studies template	☐
Editorials	• Reference list of editorial articles (or a document stating none found)	☐
	• Copies of editorial articles	☐
New data	• Reference list of new data (or statement that none available)	☐
	• Copies of new data available	☐
Validity of outcome measures	• Reference list (or statement that none available)	☐
	• Copies of validity of outcome measure references available	☐
Indirect comparison	• Copies of any indirect comparisons used in pharmacoeconomic evaluation	☐
	• Technical report	☐

Requirement	Specific items and criteria	Included
	Economic information	
Pharmacoeconomic evaluation: Technical report	• Pharmacoeconomic evaluation for the full population identified in the indication(s) to be reviewed by CADTH	☐
	• Treatment effect measures should generally not use composite endpoints	☐
	• Scenario analysis of the population identified in the reimbursement request (if different from the population in the full indication)	☐
	• Economic evaluation is a cost-utility analysis	☐
	• Base case reflects the public health care payer perspective	☐
	• 1.5% discount rate on costs and QALYs	☐
	• All relevant comparators have been included	☐
	• All results are presented probabilistically	☐
	• All ICERs reported sequentially if more than one comparator is presented	☐
	• Results are presented in disaggregated format	☐
	• Treatment effect measures generally should not use composite endpoint data	☐
	• If relevant, a graph with Kaplan-Meier curve and parametric distributions for each relevant outcome	☐
	• If relevant, companion diagnostic test information incorporated	☐
	• Alignment between the pharmacoeconomic evaluation technical report and the economic model	☐
Economic model	• Model is programmed in Excel	☐
	• Model is fully unlocked and executable, and all code is provided	☐
	• Model functions in a standalone environment and does not require access to a web-based platform	☐
	• Probabilistic analyses runs without error	☐
	• Results of the probabilistic analysis are stable (congruence test provided)	☐
	• Where there are multiple comparators, the model runs treatments simultaneously and results of all comparators are presented	☐
Supporting documentation	• Model user guide	☐
	• Indirect comparison technical report	☐
	• Unpublished studies or analyses used in the pharmacoeconomic evaluation	☐
	• Document summarizing key sources of information for the companion diagnostic test	☐

Requirement	Specific items and criteria	Included
Budget impact analysis		
Budget impact analysis: technical report	• Base case reflects pan-Canadian (national) perspective (excluding Quebec)	☐
	• Base case reflects the Health Canada-approved indication	☐
	• Scenario analysis of the reimbursement request population (if different from the Health Canada-approved indication)	☐
	• Base-case analysis uses a four-year time horizon (including the 12 months before the public funding of the drug under review for the indication being evaluated)	☐
	• Analyses presented deterministically	☐
	• All relevant comparators included	☐
	• Submitted price per smallest dispensable unit used	☐
	• Report includes at minimum decision problem, methods, assumptions and results	☐
Budget impact model	• Model is programmed in Excel	☐
	• Model is fully unlocked and executable, and all code is provided.	☐
	• Model functions in a standalone environment and does not require access to a web-based platform	☐
	• Model is flexible and allows assessment for each individual drug program	☐
	• Input values specific to the individual drug program	☐
	• Breakdown of costs by perspective reported within the submitted model	☐
	• Alignment between the technical report and the model	☐
Supporting documentation	• Reference list of all supporting documentation used and/or cited in BIAs	☐
	• Unpublished studies or analyses used to inform the budget impact analysis	☐
Reimbursement status of comparators	• A completed template summarizing the reimbursement status of all appropriate comparators (for all submissions filed on or after March 2, 2020).	☐
Epidemiologic information		
Disease prevalence and incidence	• Disease prevalence and incidence with specified breakdown (if available)	☐
	• Document is referenced	☐
Pricing and distribution information		
Price and distribution method	• Submitted unit pricing to four decimal places	☐
	• Method of distribution	☐
Implementation plan	• Completed implementation plan template	☐
Companion diagnostic(s)		
Companion diagnostics	• Reference list	☐
	• Copies of articles that highlight the clinical utility of the companion diagnostic(s)	☐
	• Disclosable price for the companion diagnostic(s)	☐

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E. Category 1 Requirements for a Plasma Protein Product Filed on a Pre-NOC Basis

Requirement	Specific items and criteria	Included
General information		
Application overview	• Completed application overview template	☐
Signed cover letter	• Clear description of submission filed	☐
	• The indication(s) to be reviewed by CADTH	☐
	• Requested reimbursement conditions, if applicable	☐
	• Names and contact information for primary and backup contacts	☐
Executive summary	• Completed executive summary template for a submission	☐
	• Maximum five pages (excluding references)	☐
	• Document is referenced	☐
Product monograph	**At the time of filing:**	
	• A copy of the most recent draft product monograph	☐
	After NOC or NOC/c is issued:	
	• Draft product monograph with tracked clinical and label review changes up to time of Health Canada approval	☐
	• Clean and dated version of Health Canada-approved product monograph	☐
Declaration letter	• Completed declaration letter template	☐
Health Canada documentation		
NOC	**At the time of filing:**	
	• A placeholder document indicating the anticipated NOC date for the indications(s) to be reviewed by CADTH	☐
	After NOC or NOC/c is issued:	
	• Copy of NOC or NOC/c granted for the indication(s) under review	☐
	• Letter of Undertaking (only if NOC/c granted)	☐
Clarimails/clarifaxes	**At time of filing:**	
	• Summary table of clinical Clarimails/Clarifaxes up to time of filing	☐
	Ongoing basis until NOC or NOC/c is issued:	
	• Revised clinical Clarimail/Clarifax summary table(s)	☐
Efficacy, effectiveness, and safety information		
Common technical document	• Section 2.5	☐
	• Section 2.7.1	☐
	• 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 of key clinical studies and any errata	☐
	• Copies of studies addressing key clinical issues	☐
	• Copies of any errata (or a document stating that none found)	☐
Clinical study reports	• Complete clinical study reports for all pivotal studies as well as other studies that address key clinical issues (if submission is filed on or after March 2, 2020)	☐

Requirement	Specific items and criteria	Included
Table of studies	• Completed table of studies template	☐
Editorials	• Reference list of editorial articles (or document stating none found)	☐
	• Copies of editorial articles	☐
New data	• Reference list of new data (or statement that none available)	☐
	• Copies of new data available	☐
Validity of outcome measures	• Reference list (or statement that none available)	☐
	• Copies of validity of outcome measure references available	☐
Indirect comparison	• Copies of any indirect comparisons used in pharmacoeconomic evaluation	☐
	• Technical report	☐
Economic information		
Pharmacoeconomic evaluation	• Pharmacoeconomic evaluation for the full population identified in the indication(s) to be reviewed by CADTH	☐
	• Scenario analysis of the population identified in the reimbursement request (if different from the population in the full indication)	☐
	• Economic evaluation is a cost-utility analysis	☐
	• Base case reflects the public health care payer perspective	☐
	• 1.5% discount rate on costs and QALYs	☐
	• All relevant comparators have been included	☐
	• Submitted price per smallest dispensable unit used	☐
	• All results are presented probabilistically	☐
	• All ICERs reported sequentially if more than one comparator is presented	☐
	• Results are presented in disaggregated format	☐
	• Treatment effect measures should generally not use composite endpoints	☐
	• If relevant, a graph with Kaplan-Meier curve and parametric distributions for each relevant outcome	☐
	• If relevant, companion diagnostic test information incorporated	☐
	• Alignment between the pharmacoeconomic evaluation technical report and the economic model	☐
Economic model	• Model is programmed in Excel	☐
	• Model is fully unlocked and executable, and all code is provided	☐
	• Model functions in a standalone environment and does not require access to a web-based platform	☐
	• Probabilistic analyses runs without error	☐
	• Results of the probabilistic analysis are stable (congruence test provided)	☐
	• Where there are multiple comparators, the model runs treatments simultaneously and results of all comparators are presented	☐
Supporting documentation	• Model user guide	☐
	• Indirect comparison technical report	☐
	• Unpublished studies or analyses used in the pharmacoeconomic evaluation	☐
	• Document summarizing key sources of information for the companion diagnostic test	☐

Requirement	Specific items and criteria	Included
Budget impact analysis		
Budget impact analysis: technical report	• Base case reflects pan-Canadian (national) perspective (excluding Quebec)	☐
	• Base case reflects the Health Canada-approved (proposed) indication	☐
	• Scenario analysis of the reimbursement request population (if different from the Health Canada-approved (proposed) indication)	☐
	• Base-case analysis uses a four-year time horizon (including the 12 months before the public funding of the drug under review for the indication being evaluated)	☐
	• Analyses presented deterministically	☐
	• All relevant comparators included	☐
	• Submitted price per smallest dispensable unit used	☐
	• Report includes at minimum decision problem, methods, assumptions and results	☐
Budget impact model	• Model is programmed in Excel	☐
	• Model is fully unlocked and executable, and all code is provided	☐
	• Model functions in a standalone environment and does not require access to a web-based platform	☐
	• Model is flexible and allows assessment for each individual drug program	☐
	• Input values specific to the individual drug program	☐
	• Breakdown of costs by perspective reported within the submitted model	☐
	• Alignment between the technical report and the model	☐
Supporting documentation	• Reference list of all supporting documentation used and/or cited in BIAs	☐
	• Unpublished studies or analyses used to inform the budget impact analysis	☐
Reimbursement status of comparators	• A completed template summarizing the reimbursement status of all appropriate comparators (for all submissions filed on or after March 2, 2020).	☐
Epidemiologic information		
Disease prevalence and incidence	• Disease prevalence and incidence with specified breakdown (if available)	☐
	• Document is referenced	☐
Pricing and distribution information		
Price and distribution method	• Submitted unit pricing to four decimal places	☐
	• Method of distribution	☐
Companion diagnostic(s)		
Companion diagnostics	• Reference list	☐
	• Copies of articles that highlight the clinical utility of the companion diagnostic(s)	☐
	• Disclosable price for the companion diagnostic(s)	☐
Additional letter for submissions filed on Pre-NOC basis		
Letter for sending NOC or NOC/c to CADTH	**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)	☐

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F. Category 1 Requirements for a Plasma Protein Product Filed on a Post-NOC Basis

Requirement	Specific items and criteria	Included
General information		
Application overview	• Completed application overview template	☐
Signed cover letter	• Clear description of submission filed	☐
	• The indication(s) to be reviewed by CADTH	☐
	• Requested reimbursement conditions, if applicable	☐
	• Names and contact information for primary and backup contacts	☐
Executive summary	• Completed executive summary template for a submission	☐
	• Maximum five pages (excluding references)	☐
	• Document is referenced	☐
Product monograph	• A copy of the most current version of the Health Canada-approved product monograph	☐
Declaration letter	• Completed declaration letter template	☐
Health Canada documentation		
NOC	• A copy of the NOC or NOC/c granted for the indication(s) to be reviewed	☐
	• Letter of Undertaking (only if NOC/c granted)	☐
Clarimails/clarifaxes	• Summary table of any clinical Clarimails/Clarifaxes up to the time of NOC or NOC/c being issued	☐
Efficacy, effectiveness, and safety information		
Common technical document	• Section 2.5	☐
	• Section 2.7.1	☐
	• 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 of key clinical issues 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	• Complete clinical study reports for all pivotal studies as well as other studies that address key clinical issues (if submission is filed on or after March 2, 2020)	☐
Table of studies	• Completed table of studies template	☐
Editorials	• Reference list of editorial articles (or a document stating none found)	☐
	• Copies of editorial articles	☐
New data	• Reference list of new data (or statement that none available)	☐
	• Copies of new data available	☐
Validity of outcome measures	• Reference list (or statement that none available)	☐
	• Copies of validity of outcome measure references available	☐
Indirect comparison	• Copies of any indirect comparisons used in pharmacoeconomic evaluation	☐
	• Technical report	☐

Requirement	Specific items and criteria	Included
	Economic information	
Pharmacoeconomic evaluation: Technical report	• Pharmacoeconomic evaluation for the full population identified in the indication(s) to be reviewed by CADTH	☐
	• Treatment effect measures should generally not use composite endpoints	☐
	• Scenario analysis of the population identified in the reimbursement request (if different from the population in the full indication)	☐
	• Economic evaluation is a cost-utility analysis	☐
	• Base case reflects the public health care payer perspective	☐
	• 1.5% discount rate on costs and QALYs	☐
	• All relevant comparators have been included	☐
	• Submitted price per smallest dispensable unit used	☐
	• All results are presented probabilistically	☐
	• All ICERs reported sequentially if more than one comparator is presented	☐
	• Results are presented in disaggregated format	☐
	• Treatment effect measures generally should not use composite endpoint data	☐
	• If relevant, a graph with Kaplan-Meier curve and parametric distributions for each relevant outcome	☐
	• If relevant, companion diagnostic test information incorporated	☐
	• Alignment between the pharmacoeconomic evaluation technical report and the economic model	☐
Economic model	• Model is programmed in Excel	☐
	• Model is fully unlocked and executable, and all code is provided	☐
	• Model functions in a standalone environment and does not require access to a web-based platform	☐
	• Probabilistic analyses runs without error	☐
	• Results of the probabilistic analysis are stable (congruence test provided)	☐
	• Where there are multiple comparators, the model runs treatments simultaneously and results of all comparators are presented	☐
Supporting documentation	• Model user guide	☐
	• Indirect comparison technical report	☐
	• Unpublished studies or analyses used in the pharmacoeconomic evaluation	☐
	• Document summarizing key sources of information for the companion diagnostic test	☐

Requirement	Specific items and criteria	Included
Budget impact analysis		
Budget impact analysis: technical report	• Base case reflects pan-Canadian (national) perspective (excluding Quebec)	☐
	• Base case reflects the Health Canada-approved indication	☐
	• Scenario analysis of the reimbursement request population (if different from the Health Canada-approved indication)	☐
	• Base-case analysis uses a four-year time horizon (including the 12 months before the public funding of the drug under review for the indication being evaluated)	☐
	• Analyses presented deterministically	☐
	• All relevant comparators included	☐
	• Submitted price per smallest dispensable unit used	☐
	• Report includes at minimum decision problem, methods, assumptions and results	☐
Budget impact model	• Model is programmed in Excel	☐
	• Model is fully unlocked and executable, and all code is provided	☐
	• Model functions in a standalone environment and does not require access to a web-based platform	☐
	• Model is flexible and allows assessment for each individual drug program	☐
	• Input values specific to the individual drug program	☐
	• Breakdown of costs by perspective reported within the submitted model	☐
	• Alignment between the technical report and the model	☐
Supporting documentation	• Reference list of all supporting documentation used and/or cited in BIAs	☐
	• Unpublished studies or analyses used to inform the budget impact analysis	☐
Reimbursement status of comparators	• A completed template summarizing the reimbursement status of all appropriate comparators (for all submissions filed on or after March 2, 2020).	☐
Epidemiologic information		
Disease prevalence and incidence	• Disease prevalence and incidence with specified breakdown (if available)	☐
	• Document is referenced	☐
Pricing and distribution information		
Price and distribution method	• Submitted unit pricing to four decimal places	☐
	• Method of distribution	☐
Companion diagnostic(s)		
Companion diagnostics	• Reference list	☐
	• Copies of articles that highlight the clinical utility of the companion diagnostic(s)	☐
	• Disclosable price for the companion diagnostic(s)	☐

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

G. Category 1 Requirements for a Tailored Review Filed on a Pre-NOC Basis

Requirement	Specific items and criteria	Included
General information		
Application overview	• Completed application overview template	☐
Signed cover letter	• Clear description of submission filed	☐
	• The indication(s) to be reviewed by CADTH	☐
	• Requested reimbursement conditions, if applicable	☐
	• Names and contact information for primary and backup contacts	☐
Executive summary	• Completed executive summary template for a submission	☐
	• Maximum five pages (excluding references)	☐
	• Document is referenced	☐
Product monograph	**At the time of filing:** • A copy of the most recent draft product monograph	☐
	After NOC or NOC/c is issued: • Draft product monograph with tracked clinical and label review changes up to time of Health Canada approval	☐
	• Clean and dated version of Health Canada-approved product monograph	☐
Declaration letter	• Completed declaration letter template	☐
Submission template		
CADTH tailored review template	• Completed CADTH tailored review template	☐
Health Canada documentation		
NOC	**At the time of filing:** • A placeholder document indicating the anticipated NOC date for the indications(s) to be reviewed by CADTH	☐
	After NOC or NOC/c is issued: • Copy of NOC or NOC/c for the indication(s) under review	☐
	• Letter of Undertaking (only if NOC/c granted)	☐
Clarimails and clarifaxes	**At time of filing:** • Summary table of clinical Clarimails/Clarifaxes up to time of filing	☐
	Ongoing basis until NOC or NOC/c is issued: • Revised clinical Clarimail/Clarifax summary table(s)	☐
Bioequivalence, efficacy, and safety evidence		
Common technical document	• Section 2.5	☐
	• Section 2.7.1	☐
	• 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	☐

Requirement	Specific items and criteria	Included
Clinical study reports	• Complete clinical study reports for all pivotal studies as well as other studies that address key clinical issues (if submission is filed on or after March 2, 2020)	☐
Table of studies	• Completed table of studies template	☐
Budget impact analysis		
Budget impact analysis: technical report	• Base case reflects pan-Canadian (national) perspective (excluding Quebec)	☐
	• Base case reflects the Health Canada-approved (proposed) indication	☐
	• Scenario analysis of the reimbursement request population (if different from the Health Canada-approved (proposed) indication)	☐
	• Base-case analysis uses a four-year time horizon (including the 12 months before the public funding of the drug under review for the indication being evaluated)	☐
	• Analyses presented deterministically	☐
	• All relevant comparators included	☐
	• Submitted price per smallest dispensable unit used	☐
	• Report includes at minimum decision problem, methods, assumptions and results	☐
Budget impact model	• Model is programmed in Excel	☐
	• Model is fully unlocked and executable, and all code is provided	☐
	• Model functions in a standalone environment and does not require access to a web-based platform	☐
	• Model is flexible and allows assessment for each individual drug program	☐
	• Input values specific to the individual drug program	☐
	• Breakdown of costs by perspective reported within the submitted model	☐
	• Alignment between the technical report and the model	☐
Supporting documentation	• Reference list of all supporting documentation used and/or cited in BIAs	☐
	• Unpublished studies or analyses used to inform the budget impact analysis	☐
Disease prevalence and incidence		
Disease prevalence and incidence	• Disease prevalence and incidence with specified breakdown (if available)	☐
	• Document is referenced	☐
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 NOC or NOC/c to CADTH	**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)	☐

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

H. Category 1 Requirements for a Tailored Review Filed on a Post-NOC Basis

Requirement	Specific items and criteria	Included
General information		
Application overview	• Completed application overview template	☐
Signed cover letter	• Clear description of submission filed	☐
	• The indication(s) to be reviewed by CADTH	☐
	• Requested reimbursement conditions, if applicable	☐
	• Names and contact information for primary and backup contacts	☐
Executive summary	• Completed executive summary template for a submission	☐
	• Maximum five pages (excluding references)	☐
	• Document is referenced	☐
Product monograph	• A copy of the most current version of the Health Canada-approved product monograph	☐
Declaration letter	• Completed declaration letter template	☐
Health Canada documentation		
NOC	• Copy of NOC or NOC/c for the indication(s) to be reviewed	☐
	• Letter of Undertaking (only if NOC/c granted)	☐
Clarimails/clarifaxes	• Summary table of any clinical Clarimails/Clarifaxes up to the time of NOC or NOC/c being issued	☐
Submission template		
CADTH tailored review template	• Completed CADTH tailored review template	☐
Bioequivalence, efficacy, and safety evidence		
Common technical document	• Section 2.5	☐
	• Section 2.7.1	☐
	• Section 2.7.3	☐
	• Section 2.7.4	☐
	• Section 5.2	☐
	• Or a statement indicating any section(s) not required for the Health Canada submission	☐
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 (if submission is filed on or after March 2, 2020)	☐
Table of studies	• Completed table of studies template	☐

Requirement	Specific items and criteria	Included
Budget impact analysis		
Budget impact analysis: technical report	• Base case reflects pan-Canadian (national) perspective (excluding Quebec)	☐
	• Base case reflects the Health Canada-approved indication	☐
	• Scenario analysis of the reimbursement request population (if different from the Health Canada-approved indication)	☐
	• Base-case analysis uses a four-year time horizon (including the 12 months before the public funding of the drug under review for the indication being evaluated)	☐
	• Analyses presented deterministically	☐
	• All relevant comparators included	☐
	• Submitted price per smallest dispensable unit used	☐
	• Report includes at minimum decision problem, methods, assumptions and results	☐
Budget impact model	• Model is programmed in Excel	☐
	• Model is fully unlocked and executable, and all code is provided	☐
	• Model functions in a standalone environment and does not require access to a web-based platform	☐
	• Model is flexible and allows assessment for each individual drug program	☐
	• Input values specific to the individual drug program	☐
	• Breakdown of costs by perspective reported within the submitted model	☐
	• Alignment between the technical report and the model	☐
Supporting documentation	• Reference list of all supporting documentation used and/or cited in BIAs	☐
	• Unpublished studies or analyses used to inform the budget impact analysis	☐
Disease prevalence and incidence		
Disease prevalence and incidence	• Disease prevalence and incidence with specified breakdown if available	☐
	• Document is referenced	☐
Pricing and distribution information		
Price and distribution method	• Submitted unit pricing to four decimal places	☐
	• Method of distribution	☐

CDR = CADTH Common Drug Review; NOC = Notice of Compliance; NOC/c = Notice of Compliance with conditions.

I. Category 1 Requirements for All Resubmission Types

Section	Specific items and criteria	Included
General information		
Application overview	• Completed application overview template	☐
Signed cover letter	• Clear description of resubmission being filed	☐
	• The indication(s) to be reviewed	☐
	• Requested reimbursement conditions, if applicable	☐
	• Names and contact information for primary and backup contacts	☐
Executive summary	• Completed executive summary template for a resubmission	☐
	• Maximum five pages (excluding references)	☐
	• Document referenced with all supporting references	☐
Product monograph	• A copy of the most current version of the Health Canada-approved product monograph	☐
Declaration letter	• Completed declaration letter template	☐
New and updated efficacy and/or safety information		
New clinical studies	• Reference lists of all new clinical studies and errata, (or r document stating none is available) included in the resubmission that were not provided in the initial submission, or a previous resubmission	☐
	• Copies of all new clinical information and errata	☐
Clinical study reports	• Complete clinical study reports for all pivotal studies as well as other studies that address key clinical issues (if submission is filed on or after March 2, 2020)	☐
Editorials	• Reference list of editorial articles (or document stating none found)	☐
	• Copies of editorial articles	☐
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	☐

Section	Specific items and criteria	Included
	New and updated economic information	
Pharmacoeconomic evaluation: Technical report	• Pharmacoeconomic evaluation for the full population identified in the indication(s) to be reviewed by CADTH	☐
	• Treatment effect measures should generally not use composite endpoints	☐
	• Scenario analysis of the population identified in the reimbursement request (if different from the population in the full indication)	☐
	• Economic evaluation is a cost-utility analysis	☐
	• Base case reflects the public health care payer perspective	☐
	• 1.5% discount rate on costs and QALYs	☐
	• All relevant comparators have been included	☐
	• Submitted price per smallest dispensable unit used	☐
	• All results are presented probabilistically	☐
	• All ICERs reported sequentially if more than one comparator is presented	☐
	• Results are presented in disaggregated format	☐
	• Treatment effect measures generally should not use composite endpoint data	☐
	• If relevant, a graph with Kaplan-Meier curve and parametric distributions for each relevant outcome	☐
	• If relevant, companion diagnostic test information incorporated	☐
	• Alignment between the pharmacoeconomic evaluation technical report and the economic model	☐
Economic model	• Model is programmed in Excel	☐
	• Model is fully unlocked and executable, and all code is provided	☐
	• Model functions in a standalone environment and does not require access to a web-based platform	☐
	• Probabilistic analyses runs without error	☐
	• Results of the probabilistic analysis are stable (congruence test provided)	☐
	• Where there are multiple comparators, the model runs treatments simultaneously and results of all comparators are presented	☐
Supporting documentation	• Required economic model supporting documentation	☐
	• Model user guide	☐
	• Indirect comparison technical report	☐
	• Unpublished studies or analyses used in the pharmacoeconomic evaluation	☐
	• Document summarizing key sources of information for the companion diagnostic test	☐

Section	Specific items and criteria	Included
Budget impact analysis		
Budget impact analysis: technical report	• Base case reflects pan-Canadian (national) perspective (excluding Quebec)	☐
	• Base case reflects the Health Canada-approved indication	☐
	• Scenario analysis of the reimbursement request population (if different from the Health Canada-approved indication)	☐
	• Base-case analysis uses a four-year time horizon (including the 12 months before the public funding of the drug under review for the indication being evaluated)	☐
	• Analyses presented deterministically	☐
	• All relevant comparators included	☐
	• Submitted price per smallest dispensable unit used	☐
	• Report includes at minimum decision problem, methods, assumptions and results	☐
Budget impact model	• Model is programmed in Excel	☐
	• Model is fully unlocked and executable, and all code is provided	☐
	• Model functions in a standalone environment and does not require access to a web-based platform	☐
	• Model is flexible and allows assessment for each individual drug program	☐
	• Input values specific to the individual drug program	☐
	• Breakdown of costs by perspective reported within the submitted model	☐
	• Alignment between the technical report and the model	☐
Supporting documentation	• Reference list of all supporting documentation used and/or cited in BIAs	☐
	• Unpublished studies or analyses used to inform the budget impact analysis	☐
Reimbursement status of comparators	• A completed template summarizing the reimbursement status of all appropriate comparators (for all resubmissions filed on or after March 2, 2020).	☐
Epidemiologic information		
Disease prevalence and incidence	• Disease prevalence and incidence data, with specified breakdown (if available)	☐
	• Document is referenced	☐
Pricing and distribution information		
Price and distribution method	• Submitted unit pricing to four decimal places	☐
	• Method of distribution	☐
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)	☐

J. Category 2 Requirements for all Submissions and Resubmissions

Requirement	Specific items and criteria	Included
BIA reports	• BIA report British Columbia	☐
	• BIA report Alberta	☐
	• BIA report Saskatchewan	☐
	• BIA report Manitoba	☐
	• BIA report Ontario	☐
	• BIA report New Brunswick	☐
	• BIA report Nova Scotia	☐
	• BIA report Prince Edward Island	☐
	• BIA report Newfoundland and Labrador	☐
	• BIA report Non-Insured Health Benefits	☐
BIA models	• BIA model British Columbia	☐
	• BIA model Alberta	☐
	• BIA model Saskatchewan	☐
	• BIA model Manitoba	☐
	• BIA model Ontario	☐
	• BIA model New Brunswick	☐
	• BIA model Nova Scotia	☐
	• BIA model Prince Edward Island	☐
	• BIA model Newfoundland and Labrador	☐
	• BIA model Non-Insured Health Benefits	☐
Supporting BIA documentation	• Reference list of all supporting documentation used and/or cited in BIAs	☐
	• Copies of all supporting documentation used and/or cited in BIAs	☐

BIA = budget impact analysis.

CADTH

Appendix 5: Electronic File Structure and Naming Format

Instructions for Sponsors

Please carefully review the following electronic file structure and naming convention before assembling the submission or resubmission requirements. If you have any questions, please email requests@cadth.ca with the complete details of your question(s).

Filing Category 1 and Category 2 Requirements:

- All materials must be submitted using Collaborative Workspaces. To file a submission, sponsors are to use the Submit and Contribute — Pharmaceutical Manufacturers function to upload the file and complete the online submission form.
- Files should be submitted as zipped (.zip) files. The maximum file size is approximately 1GB. If there are several .zip files, the number of files should be noted in the additional comments box of the submission form (e.g., file 1 of 4). The root folder(s) should be clearly named with the brand or generic drug name and submission requirement (e.g., Brand Name — Category 1).
- An email notification will be sent to the sponsor when the file has been submitted successfully.
- File names cannot exceed 64 characters or contain special characters; therefore, sponsors are required to use abbreviations as necessary.
- 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 CADTH requests additional information during the course of the review, sponsors must provide the requested information to CADTH using Collaborative Workspaces.
- The documents 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.
- File names cannot exceed 64 characters or contain special characters; therefore, sponsors are asked to use abbreviations as necessary.

A. Category 1 Requirements for a Standard Review

Represents one folder Represents one file (unlocked, searchable, and printable)

- **Brand Name – Category 1**
  - 1_Brand Name_General Information
    - 1 — Application Overview
    - 2 — Signed Cover Letter
    - 3 — Executive Summary
    - 4 — Product Monograph
    - 5 — Declaration letter
  - 2_Brand Name_Health Canada Documentation
    - 1 — Health Canada NOC
    - 2 — Letter of Undertaking (Note: only if applicable)
    - 3 — Table of Clarimails
  - 3_Brand Name_Clinical Information
    - 3.1_Common Technical Document
      - 1 — Section 2.5
      - 2 — Section 2.7.1
      - 3 — Section 2.7.3
      - 4 — Section 2.7.4
      - 5 — Section 5.2
    - 3.2_Clinical Studies and Errata
      - List of Studies and Errata
      - 1 — Trial Name_Author_Year
      - 2 — Trial Name_Author_Year Erratum
    - 3.3_Clinical Study Reports (if filed on or after March 2, 2020)
      - 1 — Trial Name
      - 2 — Trial Name
    - 3.4_Table of Studies
      - Table of Studies
    - 3.5_Editorials
      - List of Editorials
      - 1 — Author_Year
    - 3.6_New Data
      - List of New Data
      - 1 — Trial Name_Author_Year

- 3.7_Validity of Outcomes
  - List of References
  - 1 — Author_Year
- 3.8_Indirect Comparison
  - Indirect Comparison
  - Technical report
- 4_Brand Name_Economic
  - Pharmacoeconomic evaluation
  - Economic model
  - Economic model supporting documentation
- 5_Brand Name_Epidemiologic Information
  - Disease Prevalence and Incidence
  - Number Patients Accessing New Drug (Note: only if applicable)
- 6_Brand Name_Comparator Status (if filed on or after March 2, 2020)
  - Comparator Reimbursement Status
- 7_Brand Name_Pricing and Distribution
  - Pricing and Distribution
- 8_Brand Name_BIA (if filed on or after March 2, 2020)
  - 8.1_BIA Report
    - pan-Canadian BIA Report
  - 8.2_BIA Model
    - pan-Canadian BIA Model
  - 8.3_BIA Supporting Documentation
    - List of References
    - 1 — Name of document
- 9_Companion Diagnostic
  - 9.1_Clinical Utility
    - List of References
    - 1 — Author_Year
  - 9.2_Price
    - Companion Diagnostic Price

B. Category 1 Requirements for a Cell or Gene Therapy Review

Represents one folder Represents one file (unlocked, searchable, and printable)

- **Brand Name – Category 1**
- 1_Brand Name_General Information
  - 1 — Application Overview
  - 2 — Signed Cover Letter
  - 3 — Executive Summary
  - 4 — Product Monograph
  - 5 — Declaration letter
- 2_Brand Name_Health Canada Documentation
  - 1 — Health Canada NOC
  - 2 — Letter of Undertaking (Note: only if applicable)
  - 3 — Table of Clarimails
- 3_Brand Name_Clinical Information
  - 3.1_Common Technical Document
    - 1 — Section 2.5
    - 2 — Section 2.7.1
    - 3 — Section 2.7.3
    - 4 — Section 2.7.4
    - 5 — Section 5.2
  - 3.2_Clinical Studies and Errata
    - List of Studies and Errata
    - 1 — Trial Name_Author_Year
    - 2 — Trial Name_Author_Year Erratum
  - 3.3_Clinical Study Reports (if filed on or after March 2, 2020)
    - 1 — Trial Name
    - 2 — Trial Name
  - 3.4_Table of Studies
    - Table of Studies
  - 3.5_Editorials
    - List of Editorials
    - 1 — Author_Year
  - 3.6_New Data
    - List of New Data
    - 1 — Trial Name_Author_Year

- 3.7_Validity of Outcomes
  - List of References
  - Author_Year
- 3.8_Indirect Comparison
  - Indirect Comparison
  - Technical report
- 4_Brand Name_Economic
  - Pharmacoeconomic evaluation
  - Economic model
  - Economic model supporting documentation
- 5_Brand Name_Epidemiologic Information
  - Disease Prevalence and Incidence
  - Number Patients Accessing New Drug (Note: only if applicable)
- 6_Brand Name_Comparator Status (if filed on or after March 2, 2020)
  - Comparator Reimbursement Status
- 7_Brand Name_Pricing and Distribution
  - Pricing and Distribution
- 8_Brand Name_BIA
  - 8.1_BIA Report
    - pan-Canadian BIA Report
  - 8.2_BIA Model
    - pan-Canadian BIA Model
  - 8.3_BIA Supporting Documentation
    - List of References
    - 1 — Name of document
- 9_Brand Name_Implementation Plan
  - Implementation Plan
- 10_Companion Diagnostic
  - 10.1_Clinical Utility
    - List of References
    - 1 – Author_Year
  - 10.2_Price
    - Companion Diagnostic Price

C. Category 1 Requirements for a Plasma Protein Product Review

Represents one folder Represents one file (unlocked, searchable, and printable)

- **Brand Name – Category 1**
- 1_Brand Name_General Information
  - 1 — Application Overview
  - 2 — Signed Cover Letter
  - 3 — Executive Summary
  - 4 — Product Monograph
  - 5 — Declaration letter
- 2_Brand Name_Health Canada Documentation
  - 1 — Health Canada NOC
  - 2 — Letter of Undertaking (Note: only if applicable)
  - 3 — Table of Clarimails
- 3_Brand Name_Clinical Information
  - 3.1_Common Technical Document
    - 1 — Section 2.5
    - 2 — Section 2.7.1
    - 3 — Section 2.7.3
    - 4 — Section 2.7.4
    - 5 — Section 5.2
  - 3.2_Clinical Studies and Errata
    - List of Studies and Errata
    - 1 — Trial Name_Author_Year
    - 2 — Trial Name_Author_Year Erratum
  - 3.3_Clinical Study Reports (if filed on or after March 2, 2020)
    - 1 — Trial Name
    - 2 — Trial Name
  - 3.4_Table of Studies
    - Table of Studies
  - 3.5_Editorials
    - List of Editorials
    - 1 — Author_Year
  - 3.6_New Data
    - List of New Data
    - 1 — Trial Name_Author_Year

- 3.7_Validity of Outcomes
  - List of References
  - 1 — Author_Year
- 3.8_Indirect Comparison
  - Indirect Comparison
  - Technical report
- 4_Brand Name_Economic
  - Pharmacoeconomic evaluation
  - Economic model
  - Economic model supporting documentation
- 5_Brand Name_Epidemiologic Information
  - Disease Prevalence and Incidence
  - Number Patients Accessing New Drug (Note: only if applicable)
- 6_Brand Name_Comparator Status (if filed on or after March 2, 2020)
  - Comparator Reimbursement Status
- 7_Brand Name_Pricing and Distribution
  - Pricing and Distribution
- 8_Brand Name_BIA
  - 8.1_BIA Report
    - pan-Canadian BIA Report
  - 8.2_BIA Model
    - pan-Canadian BIA Model
  - 8.3_BIA Supporting Documentation
    - List of References
    - 1 — Name of document
- 9_Companion Diagnostic
  - 9.1_Clinical Utility
    - List of References
    - 1 — Author_Year
  - 9.2_Price
    - Companion Diagnostic Price

D. Category 1 Requirements for a Tailored Review Submission

Represents one folder Represents one file (unlocked, searchable, and printable)

- **Brand Name – Category 1**
- 1_Brand Name_General Information
  - 1 — Application Overview
  - 2 — Signed Cover Letter
  - 3 — Executive Summary
  - 4 — Product Monograph
  - 5 — Declaration Letter
- _Brand Name_Health Canada Documentation
  - 1 — Health Canada NOC
  - 2 — Letter of Undertaking (Note: only if applicable; adjust following file numbers if necessary)
  - 3 — Table of Clarimails
- 3_Brand Name_Submission Template
  - 1 — CDR Tailored Review Submission Template
- 4_Brand Name_Clinical Information
  - 4.1_Common Technical Document
    - 1 — Section 2.5
    - 2 — Section 2.7.1
    - 3 — Section 2.7.3
    - 4 — Section 2.7.4
    - 5 — Section 5.2
  - 4.2_Source Documentation
    - List of Documentation
    - 1 — Name_Year
    - 2 — Name_Year
  - 4.3_Clinical Study Reports (if filed on or after March 2, 2020)
    - 1 — Trial Name
    - 2 — Trial Name
  - 4.4_Table of Studies
    - Table of Studies
- 5_Brand Name_Epidemiologic Information
  - Disease Prevalence and Incidence

- 6_Brand Name_Pricing and Distribution
  - Pricing and Distribution
- 7_Brand Name_BIA (if filed on or after March 2, 2020)
  - 7.1_BIA Report
    - pan-Canadian BIA Report
  - 7.2_BIA Model
    - pan-Canadian BIA Model
  - 7.3_BIA Supporting Documentation
    - List of References
    - 1 — Name of document
- 8_Companion Diagnostic
  - 8.1_Clinical Utility
    - List of References
    - 1 — Author_Year
  - 8.2_Price
    - Companion Diagnostic Price

E. Category 1 Requirements for Resubmissions

Represents one folder Represents one file (unlocked, searchable, and printable)

- **Brand Name – Category 1**
- 1_Brand Name_General Information
  - 1 — Application Overview
  - 2 — Signed Cover Letter
  - 3 — Executive Summary
  - 4 — Product Monograph
  - 5 — Declaration letter
- 2_Brand Name_New Clinical Information
  - 2.1_New Clinical Studies
    - List of New Clinical Studies
    - 1 — Trial Name_Author_Year
    - 2 — Trial Name_Author_Year
  - 2.2_Clinical Study Reports (if filed on or after March 2, 2020)
    - 1 — Trial Name
    - 2 — Trial Name
  - 2.2_ New Editorials and Errata
    - List of Editorials and Errata
    - No Editorials or No Errata (Note: placeholder document, only if applicable)
    - 1 — Author_Year_Editorial
    - 2 — Trial Name_Author_Year_Erratum
  - 2.3_Validity of Outcomes
    - List of References
    - 1 — Author_Year
  - 2.4_Updated Table of Studies
    - Table of Studies
- 3_Brand Name_Economic
  - Pharmacoeconomic evaluation
  - Economic model
  - Economic model supporting documentation
- 4_Epidemiologic Information
  - Disease Prevalence and Incidence
- 5_Brand Name_Comparator Status (if filed on or after March 2, 2020)
  - Comparator Reimbursement Status

- 6_Brand Name_Pricing and Distribution
  - Pricing and Distribution
- 7_Brand Name_BIA (if filed on or after March 2, 2020)
  - 7.1_BIA Report
    - pan-Canadian BIA Report
  - 7.2_BIA Model
    - pan-Canadian BIA Model
  - 7.3_BIA Supporting Documentation
    - List of References
    - 1 — Name of document

F. Category 2 Requirements for all Submissions and Resubmissions

Represents one folder

Represents one file (unlocked, searchable, and printable)

- **Brand Name – Category 1**
  - 2_Brand Name BIAs
    - 2.1_BIA Reports
      - 1 — BIA Report BC
      - 2 — BIA Report AB
      - 3 — BIA Report SK
      - 4 — BIA Report MB
      - 5 — BIA Report ON
      - 6 — BIA Report NB
      - 7 — BIA Report NS
      - 8 — BIA Report PEI
      - 9 — BIA Report NL
      - 10 — BIA Report NIHB
    - 2.2_BIA Models
      - 1 — BIA Model BC
      - 2 — BIA Model AB
      - 3 — BIA Model SK
      - 4 — BIA Model MB
      - 5 — BIA Model ON
      - 6 — BIA Model NB
      - 7 — BIA Model NS
      - 8 — BIA Model PEI
      - 9 — BIA Model NL
      - 10 — BIA Model NIHB
    - 2.3_BIA Supporting Documentation
      - List of References
      - 1 — Name of document

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 (see new active substance).

Additional Information: Any information that is requested from the sponsor by CADTH in addition to the category 1 requirements that is required to complete the review of the submission or resubmission, or to clarify information related to the submission or resubmission.

Sponsor: A person, corporation, or entity eligible to file an application for a submission or resubmission to CADTH. The sponsor could be a manufacturer, a supplier, a corporation, or entity recruited by the sponsor or the supplier.

Application: Written documentation filed by a sponsor to have a drug reviewed through CADTH's drug reimbursement review processes.

Appropriate Comparator: Typically, a drug listed by one or more drug plans for the indication under review. However, the choice of appropriate comparator(s) in reviews by CADTH 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), demonstrating 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).

Budget Impact Analysis (BIA): A forecast of the impact of listing a drug on the drug plans' expenditures.

Business Day: Any day (other than a Saturday, Sunday, statutory holiday, or company holiday) on which the CADTH office in Ottawa (Ontario, Canada) is open for business during regular business hours. Please refer to the CADTH website "Contact Us" section for a listing of the CADTH Holiday Schedule.

Business Hours: Any weekday (excluding statutory and company holidays) from 8:00 a.m. to 4:00 p.m. Eastern time.

CADTH Review Team: A team assembled by CADTH to undertake the review of a submission or resubmission, or to prepare a report in response to a request for advice. The review team may include CADTH staff, contracted reviewers, and external experts with appropriate qualifications and expertise.

Calendar Days: All days including Saturday, Sunday, statutory holidays, and company holidays.

Canadian Drug Expert Committee (CDEC): An appointed, national, independent advisory committee to CADTH that makes drug-related recommendations and provides drug-related

advice through the CDR and therapeutic review processes. CDEC is composed of individuals with expertise in drug therapy, drug evaluation and drug utilization, and public members to bring a lay perspective. CDEC replaced the Canadian Expert Drug Advisory Committee (CEDAC) in September 2011.

Committee Brief: A compilation of the materials regarding a drug under review by CADTH, prepared by CADTH staff for the members of the expert committee.

Final Recommendation: A document that provides guidance to the drug programs participating in CADTH's drug reimbursement review processes to make a reimbursement decision regarding the drug under review. Final recommendations are non-binding to the drug plans. Each drug plan makes its own drug-listing decisions based on the recommendation from CADTH in addition to other factors, including the plan's mandate, jurisdictional priorities, and financial resources.

Canadian Expert Drug Advisory Committee (CEDAC): CEDAC was replaced by the CADTH Canadian Drug Expert Committee (CDEC) in September 2011. CEDAC was a CADTH advisory body composed of individuals with expertise in drug therapy and drug evaluation and public members. For drugs reviewed through the CDR process, CEDAC made formulary listing recommendations for use by the participating federal, provincial, and territorial publicly funded drug plans.

Cancelled Review: The cessation of the review of a submission or resubmission before all steps of the review process are completed. Work on a cancelled submission or resubmission does not resume.

Common Drug Review Process: A drug reimbursement review process by which CADTH conducts an objective, rigorous, evidence-based, Health Technology Assessment of the relative therapeutic merits and cost-effectiveness of drugs, incorporating patient group–submitted input.

Queuing: Queuing is a delay in the initiation of the review of a submission or resubmission by CADTH.

Companion Diagnostic Test: A companion diagnostic test is 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.

Conflict of Interest Guidelines: The conflict of interest guidelines adopted by CADTH.

Date of Acceptance for Review: The date on which CADTH has confirmed with the sponsor that the key requirements for initiating the review process for a submission or resubmission have been met.

Date of Filing: The date on which a submission or resubmission is received by CADTH.

Date of Initiation of a Review: The date on which the assigned CADTH 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 (or will be granted in the case of a submission filed on a pre-Notice of Compliance [NOC] basis), a Health Canada NOC or Notice of Compliance with conditions (NOC/c), and is approved for human use.

Drug Programs: The federal, provincial, and territorial drug programs participating in CADTH's drug reimbursement review processes.

Embargo Period: Refers to the period of time following the issuance of an draft recommendation, during which the draft recommendation is neither acted on by drug plans nor is publicly available.

Draft Recommendation: An evidence-based recommendation issued by CADTH. The draft recommendation is released to the sponsor and drug plans only, and is not publicly available. The sponsor must maintain the confidentiality of this document.

External Expert: An individual with appropriate qualifications and expertise required for some aspect of the review of the submission or resubmission, and whose services are obtained on a contract basis, as required.

Formulary: A list of drugs covered as benefits, as determined by each federal, provincial, and territorial drug plan.

Formulary Working Group (FWG): A working group of the CADTH Pharmaceutical Advisory Committee. The FWG is composed of representatives from the federal, provincial, and territorial drug plans. FWG provides advice to CADTH on pharmaceutical issues and helps with the effective jurisdictional sharing of pharmaceutical information. FWG members are observers at the expert committee meetings.

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, 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 CADTH's sdrug reimbursement review processes.

Initiation Range: Refers to time frame which submissions or resubmissions are initiated and the corresponding expert committee meeting date.

New Active Substance: A therapeutic substance that has never before 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 two or more drugs that have not been previously marketed in Canada in that combination. It may consist of either two or more new drugs, two or more previously marketed drugs, or a combination of new drug(s) and previously marketed drug(s). Combination products (funded components), a category of new combination products, contain components that are already funded by drug plans and are eligible for a tailored review by CADTH and for modified submission requirements.

New Drug: A therapeutic substance that has never before 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
- 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 submission or resubmission.

Notice of Compliance (NOC): 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 (NOC/c): 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.

Patient Group–Submitted Input: Information, submitted by a patient group, that describes the experiences and perspectives of patients living with the condition for which a drug in a submission or resubmission is indicated and the impact of drug therapy on the lives of those with that illness or condition.

Post-Notice of Compliance (NOC): The timing of filing a submission after Health Canada has granted a Notice of Compliance (NOC) or Notice of Compliance with conditions (NOC/c) for the indication(s) to be reviewed by CADTH.

Pre-Notice of Compliance (NOC): The timing of filing a submission before Health Canada has granted a Notice of Compliance (NOC) or Notice of Compliance with conditions (NOC/c) for the indication(s) to be reviewed by CADTH, and for which the anticipated date of NOC or NOC/c is within 180 calendar days of the submission being filed.

Reasons for Recommendation: These represent the key considerations and rationale used by the expert review committees in formulating the recommendation.

Request for Advice: A written request made by drug plans for expert committee advice regarding a previous final recommendation. A request for advice can result in a revised recommendation being issued by CADTH.

Request for Clarification: A written request from drug plans for clarification of an draft recommendation.

Request for Reconsideration: A written request from a sponsor for an draft recommendation to be reconsidered.

Request for Voluntary Withdrawal: A written request by a sponsor to withdraw a submission or resubmission from the review process. These may be filed any time before the final recommendation has been issued.

Resubmission: An application filed to review a previous submission or resubmission for the same indication(s) on the basis of new information after a final recommendation has been issued.

Standard Review: Consists of the CADTH review team conducting a systematic review of clinical evidence provided by the sponsor along with studies identified through its independent, systematic literature search, and an appraisal of the sponsor-provided pharmacoeconomic evaluation.

Submission: An application filed for an initial review of a drug under through CADTH's drug reimbursement review processes for a specific indication(s), for any of the following eligible drug submission types: new drug, drug with a new indication, or new combination product.

Submitted Price: The submitted price is the price per smallest dispensable unit that is submitted to CADTH and that must not be exceeded for any of the drug plans following completion of the CADTH's review. The submitted price will be disclosed in all applicable CADTH reports.

Suspended Review: Refers to the temporary cessation of the review of a submission or resubmission. This occurs if questions or issues arise outside of the regular review process or if the CADTH review team is unable to perform a thorough assessment of the submission or resubmission due to incomplete or non-transparent information. Once the issue is resolved, the review proceeds from the point at which it was suspended. The sponsor is not required to file a submission or resubmission to re-initiate the review.

Tailored Review: Consists of the CADTH review team conducting an appraisal of the clinical evidence and pharmacoeconomic evaluation filed by the sponsor using a CADTH-provided review template that is specific to the type of drug product to be reviewed.

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 [ACEIs]) in order 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.