Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

CADTH

Common Drug Review Procedure and Submission Guidelines for Subsequent Entry Biologics

March 2014

Supporting Informed Decisions

TABLE OF CONTENTS

Abbreviations

BIA	Budget Impact Analysis
BSEAR	Biologics Safety and Efficacy Assessment Report
CADTH	Canadian Agency for Drugs and Technologies in Health
CDEC	Canadian Drug Expert Committee
CDR	Common Drug Review
CEDAC	Canadian Expert Drug Advisory Committee
CPID	Certified Product Information Document
CTD	Common Technical Document
F/P/T	federal, provincial, territorial
NOC	Notice of Compliance
NOC/c	Notice of Compliance with Conditions
pCODR	pan-Canadian Oncology Drug Review
SEB	subsequent Entry Biologic

1. Foreword

1.1 About This Document

The purpose of the *Common Drug Review Procedure and Submission Guidelines for Subsequent Entry Biologics* is two-fold:

- To provide an overview of the Common Drug Review (CDR) procedure for conducting reviews of subsequent entry biologics (SEBs).
- To provide guidance to manufacturers in the preparation of CDR submissions for SEBs.

This document must be read in conjunction with the *Procedure for Common Drug Review (January 2013)*, the *Common Drug Review Submission Guidelines for Manufacturers* (January 2013) and all relevant issues of the *CDR Update*.

All references to number of days in this document are in business days unless otherwise specified. Key terms used in this document can be found defined in Appendix 2 of the *Common Drug Review Submission Guidelines for Manufacturers* (January 2013).

1.2 Overview of the Common Drug Review

The Canadian Agency for Drugs and Health Technologies in Health (CADTH) through the CDR process undertakes reviews of drug submissions, resubmissons, and Requests for Advice and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial (F/P/T) drug plans (herein referred to as "drug plans"), with the exception of Quebec's. CDR formulary listing recommendations are evidence-based and consider the relative therapeutic merits of drugs and their cost-effectiveness. Patient group input is also incorporated into the CDR process to inform the CDR assessments of drug submissions and resubmissons, and the development of Canadian Drug Expert Committee (CDEC) listing recommendations.

The objectives of the CDR process are to reduce duplication, maximize the use of limited resources and expertise, and enhance the consistency and quality of drug reviews. The target time frames for the CDR process are presented in Table 1. Please consult the *Procedure for Common Drug Review (January 2013)* for additional information regarding communications and conflict of interest as well as confidentiality guidelines (page 2).

A review team prepares evidence-based Clinical and Pharmacoeconomic Drug Review Reports, based on material submitted by manufacturers and studies identified through independent, systematic literature searches. Although the names of the review team members are not disclosed, the make-up of the review team is reported in the CDR Clinical and Pharmacoeconomic Review Reports.

CDEC is an appointed, national, independent advisory body to CADTH composed of individuals with expertise in drug therapy, drug evaluation and drug utilization, as well as public members to bring a lay perspective.[1] CDEC uses the Clinical and Pharmacoeconomic Drug Review Reports and patient input to evaluate the comparative benefits and costs of drugs to make common formulary listing recommendations to the drug plans. In addition to making listing recommendations, CDEC also provides other drug-related recommendations or advice, based on CADTH reviews, to inform decisions and strategies, including the optimal use of drugs in Canada.

[1] CDEC replaced the Canadian Expert Drug Advisory Committee (CEDAC) in September 2011.

It is important to note that each of the drug plans subsequently makes its own drug-listing decisions based on the CDEC Final Recommendations in addition to other factors, including the plan's mandate, priorities, and resources. Each plan is responsible for independently advising the manufacturer of its final listing decision and the coverage status of the drug.

Table 1: Targeted Time Frames for Key Milestones in the CDR Process

Phase of Review	Key Milestone	Business Days
Screening and Administration	• Category 1 requirements received by CADTH	0
	• Category 1 requirements screened	5 or 10[a]
	• Additional copies of submission received by CDR	5
	• Submission received by CDR reviewers	3
Order of Review	• Determining the order and timing for initiating a review	Variable[b]
Review of Submission	• Review initiated • Protocol developed • Draft CDR Clinical and Pharmacoeconomic Review Reports prepared • Review reports sent to manufacturer for comments	45
	• Manufacturer sent draft CDR review reports for comments • Manufacturer's comments sent to CDR	3 to 7
	• CDR Reviewers' responses to manufacturer's comments prepared • Final CDR Clinical and Pharmacoeconomic Review Reports prepared	3 to 7
CDEC Deliberation and Recommendation	• CDEC Brief completed • CDEC Brief sent to CDEC and participating drug plans	5
	• CDEC meeting (placement on CDEC agenda)	10 to 40
	• Embargoed recommendation document drafted • Embargoed recommendation sent to participating drug plans and manufacturer	5 to 7
Embargo Period and Options	Embargo Period[c] During the embargo period, the following scenarios may occur:	10 to 30[d]
	• Request for clarification at drug plans' request; **OR**	Variable[e]
	• Request for reconsideration at manufacturer's request; **OR**	Variable[e]
	• Resubmission based on reduced price at manufacturer's request; **OR**	Variable[e]
	• No request for clarification AND no request for reconsideration or resubmission based on reduced price	—
Finalizing and Posting Recommendation and Reports	• CDEC final recommendation drafted	5
	• CDEC final recommendation issued to drug plans and manufacturer	
	• CDEC final recommendation posted on CADTH website	Variable
	• Final CDR Clinical and Pharmacoeconomic Review Reports posted	Variable

[a] The screening period is 5 business days for submissions and 10 business days for resubmissions.
[b] Submissions and resubmissions are generally reviewed on a first-come, first served basis.
[c] The CDEC Recommendations are to be held in confidence by all stakeholders and not acted upon until after CADTH has issued the Notice of Final Recommendation accompanied by the CDEC Final Recommendation.
[d] A manufacturer may request an extension of up to 20 extra business days solely for the purpose of preparing and filing a request for reconsideration (i.e., a total of 30 business days).
[e] The time frame required to address a request for clarification, a request for reconsideration, or a resubmission based on reduced price during the embargo period depends on the amount of work required to address the request and the available dates for CDEC meetings.

2. Overview of the CDR Procedure for Subsequent Entry Biologics

2.1 Eligible Submissions for Subsequent Entry Biologic

A subsequent entry biologic (SEB) is a biologic drug that enters the Canadian market subsequent to a biologic already authorized in Canada or an authorized non-Canadian biologic drug from a jurisdiction that has an established relationship with Health Canada (i.e., a "reference product"), with which it demonstrates a high degree of similarity.

Submissions for oncology drugs used for the active treatment of cancer should be filed with the pan-Canadian Oncology Drug Review (pCODR) process.

2.2 Content of the SEB Submissions

A submission from a manufacturer must adhere to the content, format, and organization guidelines stipulated in the *Common Drug Review Submission Guidelines for Subsequent Entry Biologics.*

2.3 Patient Group Input

CADTH is finalizing the process for patient group input for SEB submissions and will communicate the final process to stakeholders once it has been completed and approved by the drug plans.

2.4 CDR Review of the SEB Submission

For a CDR review of an SEB submission, the following will apply:

- The review team validates and comments on the information provided by the manufacturer in the SEB template.
- The review team includes its assessment and appraisal of the submitted information and comments directly into the template, which then becomes the combined clinical and pharmacoeconomic review report. During this stage, the review team considers whether it needs additional information from the manufacturer. If so, CADTH will contact the manufacturer. Any delays in providing such information will result in a corresponding delay in the completion of the review, potentially requiring placement on a later CDEC agenda.
- Depending on the volume or complexity of material to be reviewed, the CDR review team may need an extension of deadlines, in particular the time required to prepare and send the draft combined clinical and pharmacoeconomic review report to the manufacturer. The manufacturer will be notified of any extensions and reasons for the extensions.
- The distribution of the combined clinical and pharmacoeconomic review report, submission of manufacturer's comments and compilation of the CDEC Brief are carried out in accordance with the *Procedure for Common Drug Review* (January 2013).
- The combined clinical and pharmacoeconomic review report is sent to the manufacturer for comment in accordance with the *Procedure for Common Drug Review* (January 2013).

2.5 CDEC Deliberation and Recommendation Options

- SEBs will be reviewed by CDEC in accordance with section 8.0 of the *Procedure for Common Drug Review* (January 2013).
- CDEC must make a recommendation or defer if additional clarification is needed.
- A description of the recommendation options is provided in *CDR Update —Issue 91*.

2.6 Embargoed CDEC Recommendation

The embargoed CDEC Recommendation will be released to the manufacturer and drug plans in accordance with section 8.4.3 of the *Procedure for Common Drug Review* (January 2013).

2.7 Requests for Clarification

A formulary working group or drug plan request for clarification of a CDEC Recommendation will be addressed in accordance with section 8.5 of the *Procedure for Common Drug Review* (January 2013).

2.8 Request for Reconsideration of CDEC's Recommendation

A manufacturer's request for reconsideration of a CDEC Recommendation will be addressed in accordance with section 8.6 of the *Procedure for Common Drug Review* (January 2013)

2.9 Request to Submit Reduced Price During the Embargo Period

A resubmission based on a reduced price during the embargo period will be addressed in accordance with section 8.7 of the *Procedure for Common Drug Review* (January 2013) and *CDR Update – Issue 97*.

2.10 Notice of Final Recommendation

The CDEC Final Recommendation will be issued in accordance with section 9 of the *Procedure for Common Drug Review* (January 2013). The CDEC Final Recommendation document will be posted on the CADTH website.

2.11 Resubmissions for SEBs

Resubmissions filed for SEBs will be addressed in accordance with section 5 of the *Procedure for Common Drug Review* (January 2013).

2.12 Posting CDR Review Reports for SEBs

CADTH will publish the CDR Clinical and Pharmacoeconomic Review Reports on the CADTH website for all CDR submissions and resubmissons for SEBs. Manufacturers will be responsible for the identification of any confidential information in the CDR Clinical and Pharmacoeconomic Review Reports and for submitting requests for redaction before these reports are published on the CADTH website.

- All requests for redaction must be accompanied by clearly stated rationale.
- At the same time that manufacturers are asked to provide comments on the draft CDR Clinical and Pharmacoeconomic Review Reports, they will be asked to identify any confidential information and submit a request for redaction (Table 2 for timelines).

- CADTH staff will redact confidential information from Clinical and Pharmacoeconomic Review Reports, based on the *Request for Redaction of Confidential Information from the Clinical and Pharmacoeconomic Review Reports* forms completed by the manufacturer.
- The manufacturers will be sent the reports with redactions at the same time as they are sent the confidential embargoed CDEC Recommendation. At this point, the manufacturer will have 10 business days to review and confirm the redactions.
- The CDR Clinical and Pharmacoeconomic Review Reports will generally be posted at the same time as the Final CDEC Recommendation is posted on the CADTH website.
- CADTH may elect to update a previously posted report should the redacted information become available in the public domain.

Note: The CDEC members will continue to receive and consider all material provided in CDR Clinical and Pharmacoeconomic Review Reports, including confidential information, for their deliberations.
In the case of a disagreement expressed by the manufacturer regarding redactions in the CDR reports, CADTH may require additional time to resolve the disagreement in consultation with the manufacturer. This additional time could delay publication of the CDR Clinical and Pharmacoeconomic Review Reports; however, any such delays will not affect the timelines for issuing the CDEC Final Recommendation.

Table 2: Time Allotted for Reviewing and Redacting CDR Reports

Submission Type	Time Allotted for Manufacturers (business days)		
	Time for Manufacturer's Comments on CDR Reports	Additional Time to Identify Confidential Material	Total Time Available for Identifying Confidential Material
SEB Submission	7	3	10

CDR = Common Drug Review; SEB = subsequent entry biologic

2.13 Disposition of Submission and Resubmission Documents

The issuance of the Notice of Final Recommendation and the posting of the CDR Clinical and Pharmacoeconomic Review Reports by CADTH signal the completion of the CDR Review of a submission or resubmission. CADTH then undertakes the steps detailed in this section regarding the disposal and archiving of media storage devices and files associated with the review. CADTH also follows this procedure for a withdrawn submission or resubmission.

- For the completed submission or resubmission, CADTH retrieves all media storage devices from the CDR review team.

- Archiving of confidential documents is carried out, as follows:
  - CADTH retains two master copies of electronic files associated with the review of a drug, including confidential information, as follows: one copy on a CADTH server and one copy of the manufacturer-supplied media storage device in secure storage. CADTH retains these electronic copies for as long as there may be a need to consult the documents. 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 is disposed of.
  - All other copies of the manufacturer-supplied media storage devices and the electronic files associated with the review of a drug are disposed of.

- Disposal of confidential media storage devices and files is carried out as follows:
  - CADTH disposes of the extra copies of the submission or resubmission media storage devices and files, including confidential documents supplied by the manufacturer, by confidential disposal. (Note: Two master copies of electronic files associated with the review of the drug are kept on file, as described above).
  - Reviewers are requested to delete and confirm the deletion of all confidential information in their electronic files.

3. Submission Guidelines for Subsequent Entry Biologics

3.1 Notice of Compliance Status at the Time of Filing an SEB Submission

A CDR Submission for an SEB can be made either:

- on a post-Notice of Compliance (NOC) basis after the indication(s) to be reviewed by CDR has/have been granted NOC or NOC/c by Health Canada; or
- on a pre-NOC basis, when Health Canada is highly likely to issue an NOC or NOC/c for the indication(s) to be reviewed under the CDR process within 90 calendar days. This type of submission is accepted with the understanding that some submission requirements (e.g., product monograph) may not be finalized at time of filing; however, they are to be provided as soon as finalized because a CDEC Recommendation will not be issued until all required information is received. Although Health Canada cannot provide assurance that an NOC or a NOC/c will be issued on a particular date or at all, manufacturers may consider filing a submission with CADTH up to 90 calendar days in advance of an anticipated NOC or NOC/c if no significant issues have been raised by Health Canada to date during the review process.

3.2 Organization of Submission Requirements

To expedite the screening of submissions for completeness and to facilitate the efficient use of documents, manufacturers must organize the submission requirement information in the order prescribed in the Category 1 and Category 2 requirements below and following the electronic file folder format in Appendix 5: Instructions and Format for Subsequent Entry Biologic Submissions. The submission checklists used by CADTH for screening Category 1 requirements and Category 2 requirements can be found in Appendix 6. These checklists may also assist manufacturers in ensuring that all requirements have been included in the submission.

The submission requirements are grouped into Category 1, Category 2, and additional information. Where there are specific submission requirements for a submission filed on a pre-NOC versus post-NOC basis, they are delineated in the descriptions below.

3.3 Category 1 Requirements

One copy of all Category 1 requirements must be filed with CADTH as a single submission package in electronic format on a CD, DVD, or USB flash drive and deemed complete before the review can proceed. When deemed complete, the manufacturer and drug plans are apprised and steps to determine the order and timing for initiating the review commence.

The Category 1 requirements are as follows:

a) Submission Overview

- A completed submission overview template. The template can be found on the CADTH website (*Submission Overview*).

b) SEB Submission Template

- A completed template for submitting the required clinical and economic information for an SEB. The template can be found on the CADTH website (*SEB Submission Template*).

c) Signed Cover Letter

- A signed cover letter (an electronic signature is acceptable) from the applicant, providing the following information:
  - a clear description of the submission being filed (e.g., Category 1 requirements for an SEB submission filed on a post-NOC basis; Category 1 and 2 requirements for an SEB submission filed on a post-NOC basis; Category 1 requirements for an SEB submission filed on a pre-NOC basis)
  - confirmation that all of the requirements have been provided in the submission
  - the indication(s) to be reviewed
  - the date the NOC or NOC/c was issued for the indication(s) to be reviewed or, in the case of a submission filed on a pre-NOC basis, the anticipated date the NOC will be issued
  - the requested listing criteria, if applicable
  - intention to provide Category 2 requirements at least 20 business days before the targeted CDEC meeting (if not being provided with Category 1)
  - a statement confirming whether the submitted price is the current marketed price or the confidential price that will become effective following the release of the CDEC Final Recommendation
  - the names and contact information (email and phone number) for the primary and backup contact(s) that CADTH can contact regarding the submission. The manufacturer 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, by emailing requests@cadth.ca.

d) Executive Summary

A high-level summary of the submission (five pages maximum excluding reference list), following the executive summary template provided on the CADTH website (*Template for Executive Summary*).

e) Health Canada NOC or NOC/c

Submissions filed on a pre-NOC basis:

- At the time of filing the submission: a slip sheet 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) being reviewed, dated and signed by Health Canada, must be sent by email to requests@cadth.ca as soon as it is available (i.e., on the day of, or next business day, after receipt from Health Canada) along with confirmation that all Category 1 information filed with CADTH is finalized. The letter template is available in Appendix 3 and on the CADTH website.
- If the SEB receives an NOC/c for the indication(s) being reviewed by CDR: 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 requests@cadth.ca as soon as it is available.

Submissions filed on a post-NOC basis:

- A copy of the NOC or NOC/c, dated and signed by Health Canada. The NOC or NOC/c must be for the indication(s) for which the SEB is to be reviewed under the CDR process.
- If the SEB in the submission has received an NOC/c for the indication(s) to be reviewed, the manufacturer 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.

f) Product Monograph

Submissions filed on a pre-NOC basis:

- At the time of filing the submission: copy of a draft product monograph showing the company, drug brand and non-proprietary names that correspond to the anticipated NOC.
- As soon as available, sent by email to requests@cadth.ca :
  - a copy of the draft product monograph initially filed 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
  - a copy of the clean and dated product monograph approved by Health Canada.

Submissions filed on a post-NOC basis:

The current product monograph indicating the date it was approved by Health Canada, as well as the company, drug brand, and non-proprietary names that correspond to the NOC.

g) Clinical Information

Common Technical Document:

- A copy of the following documents from Modules 2 and 5 of the Common Technical Document (in Microsoft Word or searchable PDF format):
  - Module 2.3 Quality Overall Summary
  - Module 2.5 Clinical Overview
  - Module 2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods
  - Module 2.7.2 Summary of Clinical Pharmacology Studies
  - Module 2.7.3 Summary of Clinical Efficacy
  - Module 2.7.4 Summary of Clinical Safety
  - Module 2.7.6 Synopses of Individual Studies
  - Module 5.2 Tabular Listing of All Clinical Studies.

Published and Unpublished Studies:

- Copies of published and unpublished studies that address key clinical issues.
  - It is preferred that unpublished data are 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 become published during the CDR review process, manufacturers must email a copy of the published study to requests@cadth.ca, indicating that it is the published version of a previously unpublished study included in the Category 1 requirements initially submitted.
  - As specified in Appendix 5, the first file in the folder must be a reference list of the articles included in the folder.

- Copies of editorial articles and errata relating to published clinical studies provided in the submission, as per the first section of the "Table of Studies" (see template on the CADTH website).

- As specified in Appendix 5, the first file in the folder must be a reference list of the articles included in the folder.
- If there are no editorial articles or errata available, a statement confirming this must be provided.

- A tabulated list of all published and unpublished clinical studies in Microsoft Word format (i.e., doc or docx) (see the Table of Studies template provided on the CADTH website for further details).

- Search strategies used to locate published studies in medical literature databases. All search terms that were used (i.e., MESH headings and keywords) and the names of databases (e.g., MEDLINE, Embase, Cochrane, etc.) that were searched are required.
  - Search results are not required.

- A signed declaration that all known unpublished clinical studies have been disclosed. The letter template is available in Appendix 1 and on the CADTH website. If CADTH discovers undisclosed unpublished trials through other sources, this may result in the submission being placed on a later CDEC meeting agenda to allow time for the retrieval and review of the trials.

CONSORT Diagrams:

- Diagrams following the CONSORT flow diagram reporting standards or similar diagrams that document the flow of patients through trials identified as pivotal trials in Health Canada documentation, as well as any other key trials included in the submission (as per the first section of the Table of Studies; see template on the CADTH website).
- All information for the four stages of a trial (i.e., enrolment, intervention allocation, follow-up, and analysis) of the CONSORT flow diagram is required. Please consult the CONSORT web page for additional details regarding the structure and content of flow diagrams (http://www.consort-statement.org/consort-statement/flow-diagram0/).

New Data:

- Copies of new data, generated since the last date that data were reported in the studies included in the Health Canada submission. Typically, the clinical studies submitted to CDR are 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.
  - As specified in Appendix 5, the first file in the folder must be a reference list of the articles included in the folder.
  - If no new data are available, a statement confirming this must be provided.

Validity of Outcome Measures:

- Copies of references supporting the validity of primary outcome measures in clinical studies.
  - As specified in Appendix 5, the first file in the folder must be a reference list of the articles included in the folder.
  - If no references are available, a statement is required to confirm that a search was undertaken but no references were located.

h) Economic and Epidemiologic Information

- The SEB submission template contains cost tables that must be completed.

Disease Prevalence:

- The prevalence or incidence of the disease(s) or condition(s) for the indication(s) to be reviewed provided for the Canadian population, with a breakdown by participating province, territory, and First Nations' populations where available. References must be provided for this document.
- All references in the following format:
    - in-text citations numbered in their order or appearance
    - a numbered reference list in the Citing Medicine format.

i) Pricing and Availability Information

Submitted Price and Method of Distribution:

- The submitted price for the SEB, reported to four decimal places as follows:
    - price per smallest unit
    - price per smallest dispensable unit for all dosage forms, strengths, and packaging formats.

- The submitted price is the price that is effective for all drug plans. It can be the current market price in Canada or the confidential price that will become effective for all drug plans following the release of the CDEC Final Recommendation whether or not the CDEC-recommended criteria for coverage are the same as the criteria requested by the manufacturer.
- Only one price (current market price or confidential price) to four decimal places per unit is to be submitted per drug that is to be reviewed under the CDR process (i.e., only one price for all indications undergoing CDR review concurrently).
- Method of distribution to pharmacies (e.g., wholesale, direct, or other arrangements).

Commitment to Honour Confidential Price:

- If the submitted price is a confidential price that will become effective following release of the CDEC Final Recommendation, a signed commitment to honour this price for all drug plans. The letter template is provided in Appendix 4 and on the CADTH website.

j) Letter Authorizing Unrestricted Sharing of Information

A letter from the holder of the NOC or NOC/c (or from the manufacturer applying for an NOC in the case of a submission filed on a pre-NOC basis), printed on company letterhead and signed by an appropriate senior official, permitting unrestricted sharing of information regarding the drug product between and within the CDR process and:

- Participating F/P/T drug plans
- F/P/T governments, including their agencies and departments
- F/P/T health authorities, including regional health authorities
- Health Canada
- Patented Medicine Prices Review Board.

The letter template is provided in Appendix 2 and on the CADTH website.

Note: When a third party (e.g., NOC holder, manufacturer, or distributor) is involved in filing a submission, a letter is required from all of the parties that may have information regarding the product on file with Health Canada.

3.4 Other Category 1 Requirements for Submissions Filed on a pre-NOC Basis

a) Screening Acceptance Letter

- A copy of the Screening Acceptance Letter indicating that an application has been accepted by Health Canada to review the drug for sale in Canada.

b) Clarifaxes

- At time of filing the submission: a summary table of Clarifaxes relating to any clinical aspects of the Health Canada review of the drug (e.g., clinical studies; product monograph; *not* including chemistry and manufacturing-related topics) up to the time of filing. The date of each Clarifax, topic for clarification, a brief summary of the response, and date of the response must be included.
- At time of filing the submission: copies of all Clarifaxes and responses relating to any clinical aspects of the Health Canada drug review as indicated above, up to the time of filing.
- On an ongoing basis up to the point of the NOC or NOC/c being issued: copies of any further clinical Clarifaxes and responses, along with a revised Clarifax summary table, sent by email to requests@cadth.ca.

3.5 Category 2 Requirements

Category 2 requirements are used by the drug plans and are not considered as part of the CDR review or recommendation process. CADTH provides secretariat support to the drug plans by ensuring that Category 2 requirements are received in the appropriate format. When Category 2 requirements are deemed complete, it indicates that CADTH has confirmed that each of the submission requirements has been provided by the manufacturer, but it does not imply that the submitted information meets the requirements of the individual drug plans. If any of the drug plans have questions regarding the submitted Category 2 requirements, they will contact manufacturers directly.

One copy of the Category 2 requirements must be provided to CADTH as a single package in electronic format on a CD, DVD or USB flash drive, organized as specified in the Electronic File Format for SEB CDR submissions (Appendix 5). Category 2 information for SEB submissions, made on both a pre-NOC or post-NOC basis, must be provided at least 20 business days before the targeted CDEC meeting at which the submission will be considered. Incomplete Category 2 requirements will not affect placement of the submission on the targeted CDEC agenda; however, the CDEC Final Recommendation will not be issued until all Category 2 requirements have been deemed complete. Category 2 requirements may be submitted concurrently with Category 1 requirements, when available. When advised that Category 1 and 2 requirements are deemed complete, manufacturers should immediately provide the drug plans with copies of the submission as described in Appendix 1 of the *Common Drug Review Submission Guidelines for Manufacturers* (January 2013). No additional copies of Category 2 submission requirements are required by CADTH.

Category 2 requirements are as follows:

a) Cover Letter

Only if not provided at the same time as Category 1 requirements:

- A signed cover letter (an electronic signature is acceptable) from the applicant, providing the following information:
  - a clear description of the submission being filed (e.g., Category 2 requirements for an SEB submission filed on a post-NOC basis)
  - confirmation that all of the Category 2 requirements have been provided.

b) Budget Impact Analyses

- Budget impact analyses (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 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 Nova Scotia data.

  The following BIA-supporting documentation is also required:
  - all supporting information used in BIAs such as market research information or utilization reports
  - copies of all documents cited in the BIAs.

- 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.

c) Certified Product Information Document

- A completed and approved copy of the Certified Product Information Document (CPID). In lieu of the CPID, the Master Formula and Final Product Specifications documents are required.

3.6 Additional Information

Additional information consists of information that CADTH requires for completion of the review. CADTH may request additional information from Health Canada or the manufacturer. Note the manufacturer's continuing responsibility to advise CADTH of any harms or safety issues that may arise during the time the submission is under review, as detailed in the Harms and Safety Information section below.

a) Harms and Safety Information

- CADTH may request additional harms and safety information; however, the manufacturer has the responsibility of advising CADTH of all data on harms related to the drug under review (including harms and safety issues that may arise during the time that the submission is under review), and of communiqués (e.g., "Dear Doctor" letters) being prepared to alert health care professionals about safety concerns. Failure to advise CADTH of these issues or of communiqués as soon as they arise may result in CADTH readjusting and extending the usual CDR timelines in order to review this information.

b) Health Canada Reviewers' Report

- CADTH requests Health Canada's Biologics Safety and Efficacy Assessment Report (BSEAR) for each submission. To avoid delays in providing the report to CADTH, manufacturers are encouraged to request the BSEAR from Health Canada as soon as they are assured that an NOC or NOC/c will be issued, and forward the BSEAR immediately upon receipt to CADTH.
- CADTH has not included the BSEAR as a Category 1 requirement in recognition that this report is not immediately available from Health Canada at the time that the manufacturers often file submissions with CADTH.

c) 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 manufacturer. These documents should be provided in searchable electronic format (i.e., PDF or Microsoft Word).

3.7 Resubmissions for SEBs

For information regarding filing a resubmission for an SEB, please consult section 5 of the *Common Drug Review Submission Guidelines for Manufacturers* (January 2013).

Appendix 1: Template for Confirming Disclosure of All Known Unpublished Studies

[Manufacturer's letterhead]

[Date]

Director, Common Drug Review and Optimal Use of Drugs
Canadian Agency for Drugs and Technologies in Health
600-865 Carling Avenue
Ottawa, ON
K1S 5S8

Dear Director:

Reference: [Brand name, generic name]

This letter confirms that [name of manufacturer] has disclosed all unpublished studies, known to this manufacturer, including those undertaken by other companies that distribute, market, and license this drug in Canada or in other countries and those undertaken by other groups or individuals as of [date of submission].

[Signature]

[Name and title of senior company official for the manufacturer of the drug]

Appendix 2: Letter Template for Authorizing Unrestricted Sharing of Information

Before completing this letter template, applicants must note the following important information:

1. Only letters free of any restrictions are accepted by CADTH. The letter should authorize CADTH to access from, and to disclose to, the bodies named in the letter any information pertaining to the drug product at any time for the purposes of review through the CDR process. A letter with any restrictions will render the submission incomplete.
2. When a third party [e.g., NOC holder, manufacturer or distributor] is involved in filing a submission, a letter is required from all the parties that may have information regarding the product file with Health Canada.

[Manufacturer's letterhead]

[Date]

Director, Common Drug Review and Optimal Use of Drugs
Canadian Agency for Drugs and Technologies in Health (CADTH)
600-865 Carling Avenue
Ottawa, ON
K1S 5S8

Dear Director:

Reference: [Brand name, generic name]

This letter authorizes the unrestricted communication with respect to the product under review through the CDR process at the Canadian Agency for Drugs and Technologies in Health (CADTH) between CADTH and the following:

- Participating F/P/T drug plans
- F/P/T governments, including their agencies and departments
- F/P/T health authorities, including regional health authorities
- Health Canada
- Patented Medicine Prices Review Board.

[Signature]

[Name and title of senior company official for the manufacturer of the drug]

Appendix 3: Letter Template for Sending NOC or NOC/c to CADTH

Note: This letter indicates that the NOC or NOC/c is attached and confirms that all finalized Category 1 requirements for the stated submission filed on a pre-NOC basis have been provided to CADTH.

[Manufacturer's letterhead]

[Date]

Central Intake
Canadian Agency for Drugs and Technologies in Health (CADTH)
600-865 Carling Avenue
Ottawa, ON
K1S 5S8

Dear Central Intake:

Reference: [Brand name, generic name]

Attached is the Health Canada Notice of Compliance (NOC) or Notice of Compliance with Conditions (NOC/c).

This letter confirms that all Category 1 requirements filed with CADTH for the (insert brand name) submission, filed on a pre-NOC basis, are finalized. This includes the following: the Health Canada-approved product monograph (one version with changes tracked and one version that is clean); the summary table of all Clarifaxes up to the point of the NOC or NOC/c being issued; and copies of all Clarifaxes and responses up to the point of the NOC or NOC/c being issued.

[Signature]

[Name and title of senior company official for the manufacturer of the drug]

Appendix 4: Letter Template for Commitment to Honour a Confidential Price

[Manufacturer's letterhead]

[Date]

Director, Common Drug Review and Optimal Use of Drugs
Canadian Agency for Drugs and Technologies in Health
600-865 Carling Avenue
Ottawa, ON
K1S 5S8

Dear Director:

Reference: [Brand name, generic name]

This letter confirms that [name of manufacturer] will supply the above-named drug at the confidential submitted price, as provided elsewhere in this submission, to all CDR-participating drug plans.

[Signature]

[Name and title of senior company official for the manufacturer of the drug]

Appendix 5: Instructions and Format for Subsequent Entry Biologic Submissions

Instructions for Manufacturers

Please read the instructions below before assembling the submission requirements. If you have any questions regarding the CDR submission process, please email requests@cadth.ca with the complete details of your question(s).

Filing Category 1 and Category 2 Requirements:

- Please carefully review the electronic format and naming convention documented below and ensure that the submission is consistent with these guidelines.

- Documents should be organized on two CDs, DVDs, or USB flash drives, as follows:
  - Category 1 submission requirements on one CD, DVD, or USB flash drive
  - Category 2 requirements on one CD, DVD, or USB flash drive (unless being submitted at the same time as Category 1 submission requirements, in which case they can be on the same CD, DVD, USB flash drive if they all fit; otherwise provide separate media devices).

- File names cannot exceed 64 characters; therefore, manufacturers are invited to use abbreviations when necessary.

- The media devices (CDs, DVDs, or USB flash drives) used for the submission must be clearly labelled with the brand name, submission date (DD/MM/YYYY), and brief description of contents (e.g., Category 1, Category 2, Category 1 and 2).

- Documents must be provided in PDF or Microsoft Word format, unless otherwise indicated. These files must be unlocked, searchable, and printable. Users must be able to extract information or combine documents.

- Documents must be easily identified and labelled according to the format provided below.

How to File Submissions

- Submissions can be delivered to CADTH by personal delivery, by registered mail, or by courier and are to be addressed to:

  Central Intake
  Canadian Agency for Drugs and Technologies in Health (CADTH)
  600-865 Carling Avenue
  Ottawa, ON
  K1S 5S8

- When initially filing a submission, the manufacturer should deliver only one (1) complete copy of the Category 1 requirements to CADTH in electronic format on CD, DVD, or USB flash drive with all of the Category 1 requirements. See the format and naming convention documented below. The manufacturer should wait until the Category 1 submission has been deemed complete by CADTH before submitting any further copies.

- When filing Category 2 submission requirements, the manufacturer should deliver one (1) complete copy to CADTH in electronic format (CD, DVD, or USB flash drive), as specified in the format and naming convention documented below.

- When both Category 1 and 2 submission requirements have been deemed complete, the manufacturer should immediately provide copies to the drug plans as described in Appendix 1 of the *Common Drug Review Submission Guidelines for Manufacturers* (January 2013).

Providing Additional Information During the Review:

- If CADTH requests additional information during the course of a review, manufacturers can respond by providing it to CADTH by email or on a CD, DVD, or USB flash drive.
  - If the documents are less than 10 MB, they can be sent by email to the submission coordinator.
  - If the files exceed 10 MB, the documents must be provided on clearly labelled CDs, DVDs, or a USB flash drive.

- Documents must be provided in PDF or Microsoft Word format. These files must be unlocked, searchable, and printable. Users must be able to extract information or combine documents.

- File names cannot exceed 64 characters; therefore, manufacturers are invited to use abbreviations when necessary.

Electronic File Format for Subsequent Entry Biologic CDR Submissions

The following folder and file structure reflects each of the SEB CDR submission requirements and the order in which they are to be provided on the submitted CDs, DVDs or USB flash drives.

Represents one folder

Represents a PDF or Microsoft Word file (unlocked, searchable, and printable)

CD, DVD, or USB flash drive #1: Brand Name Date — Category 1

- 1_Brand Name_General Information
  - 1 - Brand Name_Submission Overview
  - 2 - Brand Name_Signed Cover Letter
  - 3 - Brand Name_Executive Summary
  - 4 - Brand Name_Health Canada NOC or NOC/c
  - 5 - Brand Name_Product Monograph

- 2_ Brand Name_SEB Submission Template
  - 1 - Brand Name_SEB Submission Template

- 3_Brand Name_Clinical Information
  - 3.1_Common Technical Document
    - 1 - Module 2.3
    - 2 - Module 2.5
    - 3 - Module 2.7.1
    - 4 - Module 2.7.2
    - 5 - Module 2.7.3
    - 6 - Module 2.7.4
    - 7 - Module 2.7.6
    - 8 - Module 5.2
  - 3.2_Articles

    The first file in the folder must be a reference list of the articles included in the folder. Each reference must be a separate document. Study file names must be short and concise. For example:
    - _List of Articles
    - 1 - Trial Name_Smith_2007
    - 2 - Trial Name_Wong_2008
  - 3.3_Editorials and Errata

    Study file names must be short and concise. For example:
    - _List of Editorials and Errata
    - 1 - Smith CMAJ 2007

- 3.4_Table of Studies
  - Table of Studies

  Note: must be submitted as a .doc or .docx file.

- 3.5_Search Strategies
  - Search Strategy

- 3.6_Brand Name_Disclosure of Studies
  - Brand Name_Signed Disclosure of Studies

- 3.7_Brand Name_CONSORT
  - 1 - CONSORT (Study X)
  - 2 - CONSORT (Study Y)

- 3.8_Brand Name_New Data

  Study file names must be short and concise. For example:
  - _List of New Data
  - 1 - Smith CMAJ 2007
  - 2 - Jones NEJM 2010

- 3.9_Brand Name_Validity of Outcomes

  Note: The first file in the folder must contain a reference list of the articles provided in support of the outcomes measures. Each reference must be a separate document.
  - _List of References
  - 1 - Smith CMAJ 2007
  - 2 - Jones NEJM 2010

- 4_Brand Name_Epidemiologic Information
  - Disease Prevalence and Incidence

- 5_Brand Name_Pricing and Availability
  - 4.1_Brand Name_Pricing and Distribution
  - 4.2_Brand Name_Commitment Confidential Price

- 6_Brand Name_Sharing of Information
  - Letter Information Sharing

- 7_Brand Name_Other Pre-NOC Info

  Note: This folder and files are ONLY for a Submission filed on a pre-NOC basis.
  - 7.1_ Screening Acceptance Letter

- 7.2_Clarifaxes
  - Clarifax Table

- Copy of Clarifax 1 and Response
- Copy of Clarifax 2 and Response

CD, DVD, or USB flash drive #2: Brand Name_Category 2

- 1_Brand Name BIAs
  - 1.1_Brand Name_BIAs
    - 1 - BIA BC
    - 2 - BIA AB
    - 3 - BIA SK
    - 4 - BIA MB
    - 5 - BIA ON
    - 6 - BIA NB
    - 7 - BIA NS
    - 8 - BIA PE
    - 9 - BIA NL
    - 10 - BIA NIHB
  - 1.2_BIA Supporting Documentation
    - _List of Supporting Documents
    - 2 - Name of Supporting Document
    - 3 - Name of Supporting Document
  - 1.3_Copies of BIA References
    - _List of References
    - 2 - Name of Reference
    - 3 - Name of Reference
- 2_Brand Name_CPID
  - CPID

Appendix 6: SEB Submission Requirement Checklists

Table A1: Category 1 Requirements for SEB Submission Filed on a Pre-NOC Basis

Section	Specific items and criteria	Included
General Information		
Overview	• Completed Submission Overview Template	
SEB Template	• Completed SEB Submission Template	
Signed Cover Letter	• Clear description of submission filed	
	• Confirmation that all requirements have been included	
	• The indication(s) to be reviewed	
	• Anticipated date of NOC for indication(s) to be reviewed	
	• Requested listing criteria, if applicable	
	• Intention to provide Category 2 requirements at least 20 business days before targeted CDEC meeting	
	• Confirmation of whether submitted price is market price or confidential price	
	• Names and contact information for primary and backup contacts	
Executive Summary	• Completed Executive Summary Template	
	• Maximum five pages (excluding references)	
	• Document referenced with all supporting references	
Notice of Compliance	• At time of filing: slip sheet in the initial submission specifying anticipated NOC date for indications(s) to be reviewed	
	• As soon as available (by email): NOC or NOC/c granted for indication(s) to be reviewed	
	• As soon as available (by email): Letter of Undertaking (only if NOC/c granted)	
Product Monograph	• At time of filing: copy of draft product monograph	
	• As soon as available (by email): draft product monograph with tracked clinical & label review changes up to time of Health Canada approval, as soon as available	
	• As soon as available (by email): clean and dated version of Health Canada approved product monograph	
Clinical Information		
Common Technical Document	• CTD Module 2.3	
	• CTD Module 2.5	
	• CTD Module 2.7.1	
	• CTD Module 2.7.2	
	• CTD Module 2.7.3	
	• CTD Module 2.7.4	
	• CTD Module 2.7.6	
	• CTD Module 5.2	
Published and Unpublished Studies	• Reference list of key clinical issues studies	
	• Copies of studies addressing key clinical issues	
	• Reference list for editorial articles/errata (or statement that none found)	
	• Copies of editorial articles and errata	
	• Table of Studies in Microsoft Word format	
	• Literature search strategy	
	• Signed declaration that all unpublished studies have been disclosed	
CONSORT Diagrams	• For pivotal trials in Health Canada submission	
	• For other key trials (as per first section of the Table of Studies)	
New Data	• Reference list (or statement that none)	

Section	Specific items and criteria	Included
	• Copies of new data available	
Validity of Outcomes	• Reference list (or statement that none available)	
	• Copies of validity of outcomes references available	
Epidemiologic Information		
Prevalence and incidence	• Disease prevalence and incidence data, with breakdown if available	
	• Document is referenced	
Pricing and Availability Information		
Price and Distribution	• Submitted unit pricing to four decimal places	
	• Method of distribution	
Letter	• Signed commitment if submitted price is confidential price	
Unrestricted Sharing of Information		
Letter	• Letter Authorizing Unrestricted Sharing of Information	
Other Pre-NOC Information		
Screening Acceptance	• Copy of screening acceptance letter	
Clarifaxes	• At time of filing: summary table of clinical Clarifaxes	
	• At time of filing: copies of Clarifaxes and responses	
	• Ongoing basis to point of NOC or NOC/c (by email): copies of further Clarifaxes and responses	
	• Ongoing basis to point of NOC or NOC/c (by email): revised Clarifax table	

CDEC = Canadian Drug Expert Committee; CTD = Common Technical Document; NOC = Notice of Compliance; NOC/c = Notice of Compliance with Conditions; SEB = Subsequent Entry Biologic

Table A2: Category 1 Requirements for SEB Submission Filed on a Post-NOC Basis

Section	Specific items and criteria	Included
General Information		
Overview	• Completed Submission Overview Template	
SEB Template	• Completed SEB Submission Template	
Signed Cover Letter	• Clear description of submission filed	
	• Confirmation that all requirements have been included	
	• The indication(s) to be reviewed	
	• Date NOC or NOC/c issued for indication(s) to be reviewed	
	• Requested listing criteria, if applicable	
	• Intention to provide Category 2 requirements at least 20 business days before targeted CDEC meeting	
	• Confirmation of whether submitted price is market price or confidential price	
	• Names and contact information for primary and backup contacts	
Executive Summary	• Completed Executive Summary Template	
	• Maximum five pages (excluding references)	
	• Document referenced with all supporting references	
Notice of Compliance	• Copy of Health Canada NOC or NOC/c for indication(s) to be reviewed	
	• Letter of undertaking (if NOC/c)	
Product Monograph	• Copy of current Health Canada-approved product monograph	
Clinical Information		
Common Technical Document	• CTD Module 2.3	
	• CTD Module 2.5	
	• CTD Module 2.7.1	
	• CTD Module 2.7.2	
	• CTD Module 2.7.3	
	• CTD Module 2.7.4	
	• CTD Module 2.7.6	
	• CTD Module 5.2	
Published and Unpublished Studies	• Reference list of key clinical issues studies	
	• Copies of studies addressing key clinical issues	
	• Reference list of editorial articles/errata (or statement that none found)	
	• Copies of editorial articles and errata	
	• Table of Studies in Microsoft Word format	
	• Literature search strategy	
	• Signed declaration that all unpublished studies have been disclosed	
CONSORT Diagrams	• For pivotal trials in Health Canada submission	
	• For other key trials (as per first section of the Table of Studies)	
New Data	• Reference list (or statement that none)	
	• Copies of new data available	
Validity of Outcomes	• Reference list (or statement that none available)	
	• Copies of validity of outcomes references available	
Epidemiologic Information		
Prevalence and incidence	• Disease prevalence and incidence data, with breakdown if available	
	• Document is referenced	
Pricing and Availability Information		

Section	Specific items and criteria	Included
Price and Distribution	• Submitted unit pricing to four decimal places	
	• Method of distribution	
Letter	• Signed commitment if submitted price is confidential price	
Unrestricted Sharing of Information		
Letter	• Letter Authorizing Unrestricted Sharing of Information	

CDEC = Canadian Drug Expert Committee; CTD = Common Technical Document; NOC = Notice of Compliance; NOC/c = Notice of Compliance with Conditions; SEB = Subsequent Entry Biologic

Table A3: Category 2 Requirements for SEB Submissions

Section	Specific items and criteria	Included
Signed cover letter	• Clear description of submission filed	
	• Confirmation that all Category 2 requirements have been included	
BIAs	• British Columbia	
	• Alberta	
	• Saskatchewan	
	• Manitoba	
	• Ontario	
	• New Brunswick	
	• Nova Scotia	
	• Prince Edward Island	
	• Newfoundland and Labrador	
	• Non-Insured Health Benefits	
Supporting BIA Documentation	• Documentation of all market research or utilization information used in BIAs	
	• Copies of all documents cited in BIAs	
CPID	• Copy of approved CPID	

BIA = Budget Impact Analysis; CPID = Certified Product Information Document