Common Drug Review Submission Guidelines for Manufacturers

January 2013

RECORD OF UPDATES

Update	Version	Reported in *CDR Update*
Original	June 2003	No. 3 — June 20, 2003
1	August 2003 (Revised August 22, 2003)	No. 4 — August 22, 2003
2	September 2003 (Revised September 16, 2003)	No. 6 — September 17, 2003
3	November 12, 2003 (Revised November 12, 2003)	No. 7 — November 19, 2003
4	November 12, 2003 (Only Appendix 1 was updated on April 19, 2004. No other changes were made to the November 12, 2003 version.)	No. 9 — April 23, 2004
5	July 2004 (Revised July 2004)	No. 12 — August 17, 2004
6	December 1, 2004 (Revised December 1, 2004)	No. 14 — December 2, 2004
7	January 25, 2005 (Revised January 25, 2005 to reflect ACP)	No. 15 — February 1, 2005
8	July 2005 (Revised July 25, 2005)	No. 20 — July 26, 2005
9	May 2006 (Revised extensively)	No. 27 — May 10, 2006
10	September 2006 (Revised September 2006)	No. 29 — September 21, 2006
11	February 2007	No. 34 — March 8, 2007
12	July 2007	No. 38 — June 29, 2007
13	October 1, 2007	No. 40 — October 1, 2007
14	October 4, 2007 (Correction in Appendix 1 to Non-Insured Health Benefits (NIHB) address)	
15	November 29, 2007 (Revised Confidentiality Guidelines)	No. 43 — November 29, 2007
16	April 2008	No. 47 — April 7, 2008
17	April 2009	No. 57 — April 21, 2009
18	July 2009	No. 60 — July 20, 2009
19	May 2010 (Patient Group Input and new Combination Products [Funded Components] added.)	No. 70 — May 14, 2010
20	August 2010	No. 72 — August 5, 2010

Update	Version	Reported in *CDR Update*
21	December 2010 (Revised Priority Review criterion)	No. 73 — December 14, 2010
22	September 2011	No. 77 — September 27, 2011
23	November 2011	No. 78 — November 15, 2011
24	January 2013	No. 85 — January 18, 2013

INQUIRIES

General inquiries and correspondence about the Common Drug Review (CDR) should be directed to:

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

Telephone: 613-226-2553
Fax: 613-226-5392
Email: requests@cadth.ca
Website: www.cadth.ca

Inquiries about specific Submissions under review should be directed to the CDR contact provided by CADTH.

Submissions should be sent to:

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

Telephone: 613-226-2553

Pre-Submission Meetings:
To facilitate the efficient preparation and filing of submissions under the CDR process, pharmaceutical manufacturers may request pre-submission meetings with CADTH to discuss submission requirements. Manufacturers are also invited to provide information on drugs in their pipeline so that CADTH may plan for future submissions. See the CADTH website at www.cadth.ca for information about Pre-submission meetings.

Pre-submission meetings may be requested by sending an email to meetingrequests@cadth.ca or calling 613-226-2553.

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1 PURPOSE

The purpose of the *Common Drug Review Submission Guidelines for Manufacturers* is two-fold:

- They provide guidance to Manufacturers in the preparation of Submissions for New Drugs, Submissions for New Combination Products, Submissions for Drugs with New Indications, Submissions for Pre-NOC (Notice of Compliance) Drugs, and for Resubmissions. The Submissions and Resubmissions must meet the needs of the Common Drug Review (CDR) process and participating federal, provincial, and territorial (F/P/T) Drug Plans.
- They provide information about the CDR processes. (Further detail about the CDR process is available in the *Procedure for Common Drug Review* in the CDR section of the Canadian Agency for Drugs and Technologies in Health [CADTH] website, www.cadth.ca.)

2 INTRODUCTION

CADTH, through the CDR process, undertakes reviews of Drug Submissions and provides formulary listing recommendations to all Canadian, publicly funded federal, provincial, and territorial (F/P/T) Drug Plans, with the exception of Quebec (Appendix 1 lists participating plans). It is administered by CADTH, a national body that provides Canada's F/P/T health care decision-makers with credible, impartial advice and evidence-based information about the effectiveness and efficiency of drugs and other health technologies. The goals of the CDR process are to reduce duplication in the performance of reviews, to maximize the use of limited resources and expertise, and to provide consistent and rigorous Drug reviews.

CDR reviews consist of an evidence-based review of the available clinical evidence and a critique of Manufacturer-submitted pharmacoeconomic evaluation. In 2010, Patient Group Input was incorporated into the CDR process to inform the CADTH assessments of Drug Submissions and the development of Canadian Expert Drug Advisory Committee (CEDAC) recommendations. As of September 2011, CEDAC was replaced by the Canadian Drug Expert Committee (CDEC).

CDEC — an appointed, national, independent body of physicians, pharmacists, other health care professionals, and public members — uses Clinical and Pharmacoeconomic Drug Reviews and Patient Group Input to evaluate the comparative benefits and costs of the Drugs under consideration and makes common formulary listing Recommendations to participating F/P/T 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.

Each of the participating F/P/T Drug Plans makes its own listing decisions based on CDEC recommendations plus other factors, including the plan's mandate, priorities, and resources. Each plan is responsible for independently advising the Manufacturer of its listing decision and the coverage status of the Drug.

An overview of the CDR review process is presented in Figure 1.

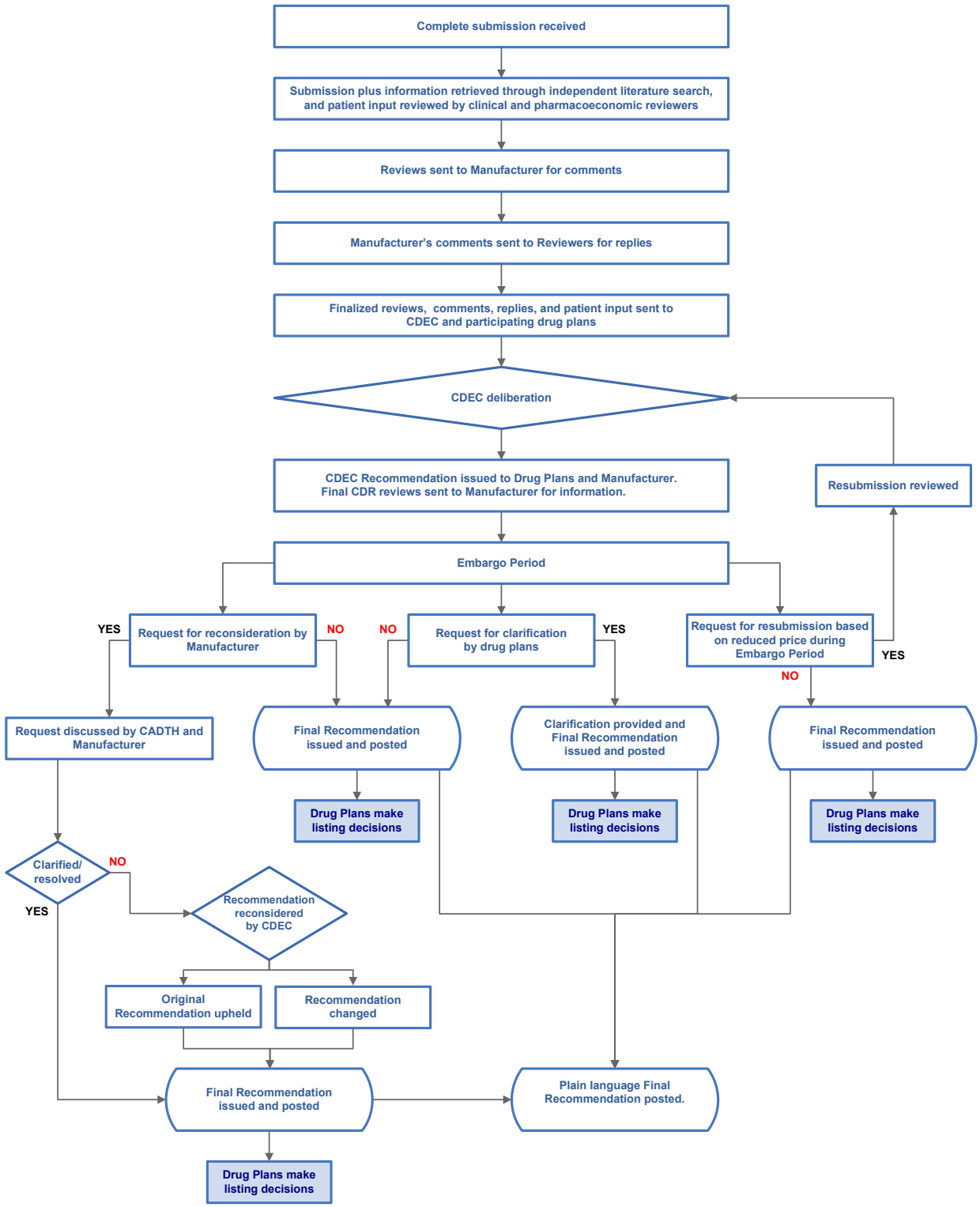
All references to number of days in this document are in Business Days, unless otherwise specified.

The capitalized terms in this document are defined in Appendix 2.

3 CHANGES TO CDR SUBMISSION GUIDELINES FOR MANUFACTURERS

CADTH may amend, from time to time, the *CDR Submission Guidelines for Manufacturers* and all matters related to CDR. The participating Drug Plans are consulted as required. Amendments to, and clarifications of, the Submission Guidelines and all related documents may be effected by means of Directives (updates) issued by CADTH.. Generally changes that are corrections or clarifications become effective immediately. Changes that are not feasible for Manufacturers to implement because they may be in the midst of filing a Submission will generally have a three (3) month grace period from the date of announcement before becoming effective.

Figure 1: CDR Process



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

4 THE SUBMISSION PROCESS

A Submission to CADTH for review through the CDR process represents a Submission to all participating F/P/T Drug Plans. A Submission from a Manufacturer must adhere to the content, format, and organization guidelines stipulated in this document.

The *Common Drug Review Submission Guidelines for Manufacturers* consolidate the requirements of the participating F/P/T Drug Plans and the requirements for the CDR process. These requirements include information that CADTH needs to undertake the Clinical and Pharmacoeconomic Reviews of Drugs and other information that Drug Plans use in making listing decisions. Participating Drug Plans have requested that CADTH assume responsibility for ensuring that all of the Submission Requirements are complete.

A Drug can undergo only one type of CDR Review during the same period. For example, if a Drug is at any stage of the review process as a Submission, it will not be reviewed concurrently as a Resubmission. An exception may be made for a Submission for a New Indication. This particular situation will be assessed on a case-by-case basis considering factors such as where in the CDR review process the Submission or Resubmission under review is, how distinct the New Indication is from the indication under review, and the resources required for the review of the New Indication.

If New Information (that is, new clinical information not previously submitted or published or new cost information that significantly impacts the cost-effectiveness of the Drug) becomes available after a Submission or Resubmission has been filed, and the Applicant wants the New Information to be considered under the CDR process, the Applicant must provide the New Information as a Resubmission. CADTH will stop its review of the Submission or Resubmission, and the Resubmission with the New Information will be placed at the end of the review queue. (Note: The Review of accepted Resubmissions based on Reduced Price during the Embargo Period proceeds as quickly as possible through the review process — i.e., it is not placed at the end of the review queue.)

4.1 Submissions

(Note: See section 5 for information regarding Resubmissions.)

4.1.1 Commencement of Process

The CDR process is initiated:

- by the Manufacturer, the Formulary Working Group (FWG), or one or more Drug Plans filing a Submission with CADTH under the CDR process; or
- by the FWG, or one or more Drug Plans, filing a Request for Advice with CADTH under the CDR process; or
- by the Manufacturer, the FWG, or one or more Drug Plans filing a Resubmission with CADTH under the CDR process.

4.1.2 Eligible Submissions from Manufacturers

Eligible Submissions from Manufacturers include New Drugs, New Combination Products, Drugs with New Indications that have received a Notice of Compliance (NOC) or a Notice of Compliance with Conditions (NOC/c) from Health Canada for the indication under review, and New Drugs with a

pending NOC or NOC/c (referred to as "Pre-NOC Submissions"). Following are descriptions of eligible Submissions. CADTH may consult with the participating Drug Plans to confirm eligibility:

- New Drugs are New Active Substances that have not been previously marketed in Canada, regardless of when the NOC or NOC/c was issued. New Drug Submissions include new salts of marketed products but do not include the following variations of existing products being funded by participating Drug Plans (line extensions) containing the same Active Substance(s):
  - New dosage forms with the same route of administration (e.g., if a drug in tablet form becomes available in capsule form, a Submission for the capsule is not required).
    Note: New parenteral products/formulations (e.g., intravenous, intramuscular, subcutaneous, etc., dosage forms) are not considered line extensions of one another as they have different routes of administration and as a result there may be potential differences in pharmacokinetics and pharmacodynamics as well as differences in cost. Manufacturers are asked to contact CADTH at Requests@cadth.ca for guidance on whether a Submission is required for parenteral line extensions.
  - 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, a Submission for the 200 mg tablet is not required).

- New Combination Products consist of two or more Drugs that have not been previously marketed in Canada in that combination. They may consist of either two or more New Drugs or two or more previously marketed Drugs or a combination of New Drug(s) and previously marketed Drug(s). Note: New Combination Products containing two or more drugs that are already funded by Drug Plans — i.e., Combination Products (Funded Components) — are eligible for a tailored review (see Section 4.4). One or more of the components may be non-prescription drugs, but at least one component must be a prescription drug. All other Combination Products undergo the regular CDR review and must be submitted in accordance with regular submission requirements.

- A Drug with a New Indication(s) is either:
  - a Drug previously reviewed by CDR that has received a NOC or NOC/c for a New Indication(s); or
  - a Drug marketed before the establishment of CDR that has received a NOC or NOC/c for a New Indication(s); and in either case the Drug with a New Indication must meet one of the following:
    - the Drug has a restricted listing in one or more Drug Plan Formularies and the Drug Plans have agreed that it should be submitted; or
    - the Drug is not listed in any of the Drug Plan Formularies and the Drug Plans have agreed that it should be submitted; or
    - the Drug Plans have requested the review of the Drug with New Indication(s).

- A Pre-NOC Submission is for a New Drug or a Drug with a New Indication for which Health Canada is highly likely to issue an NOC or NOC/c within ninety (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 the 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 NOC/c will be issued on a particular date or at all, Manufacturers may consider filing a Submission with CADTH up to ninety (90) calendar days in advance of anticipated NOC or NOC/c if no significant issues have been raised by Health Canada.

- A Post-NOC Priority Review Submission or Resubmission for a New Drug or a Drug with a New Indication must have a NOC or NOC/c and meet one of the following criteria:
  - the New Drug or Drug with a New Indication is effective for the treatment of an immediately life-threatening disease or other serious disease for which it offers substantial improvements in clinically important outcome measures of effectiveness, safety, tolerability, and/or quality of life compared with other available therapies in Canada, or for which no comparable Drug is marketed in Canada; or
  - the New Drug or a Drug with a New Indication will have a significant impact in reducing the Drug expenditures of the Drug Plans for that indication. If listed, the projected total combined savings to the participating Drug Plans must be an average of at least $2.5 million per year for the first three years the product is marketed in Canada.

  (Note: A Drug that qualifies for a Priority Review under Health Canada provisions must meet CDR Post-NOC Priority Review Criteria to be eligible for a CDR Post-NOC Priority Review.)

The FWG or one or more participating Drug Plans may request that CADTH undertake the review of Submissions, including Drugs that are not New Drugs, New Combination Products, or Drugs with New Indications. In these cases, CADTH will contact the Manufacturers for clinical and pharmacoeconomic data.

Where to File Submissions

- All New Drugs, New Combination Products, Drugs with New Indications, Pre-NOC Drugs, and Post-NOC Priority Review Submissions or Resubmissions, including HIV/AIDS Drugs and "hospital" Drugs that the participating Drug Plans want to be reviewed through CDR, should be submitted by Manufacturers to CADTH for review to be eligible for consideration for coverage by participating Drug Plans.

- While most of the participating Drug Plans cover HIV/AIDS Drugs, there are some exceptions, and guidance regarding Submissions for these agents can be found in Appendix 3.

- Submissions for oncology Drugs used for the active treatment of cancer should be filed with the pan-Canadian Oncology Drug Review.

- Submissions should continue to be made directly to Drug Plans for the following items until further notice:
  - New single source products that do not contain New Drugs
  - Line extensions of marketed products, including new dosage forms with the same route of administration and new strengths of the same dosage form. For other line extensions (including new parenteral products/formulations that are not administered through the same route of administration), contact CADTH for direction.
  - Generic products
  - Resubmissions for products reviewed prior to CEDAC.

Whenever there is doubt as to whether a Submission should be made to CADTH, Manufacturers are invited to contact CADTH for direction. CADTH may consult with the participating Drug Plans in those cases where Drugs do not clearly fall into a category described above.

4.1.3 Filing of Submissions

- Submissions or Resubmissions — with the exception of Resubmissions based on a Reduced Price during the Embargo Period, which may be submitted by email — must be delivered to CADTH by mail or courier (Appendix 4). Submissions cannot be filed electronically at this time. When initially filing a Submission, the Manufacturer should deliver only one complete copy of the Category 1 Submission Requirements to CADTH in *hard copy*, plus one complete copy on CD, DVD, or memory stick (Appendix 7F—specifications for electronic format), with all of the Submission Requirements. (Note: Three CDs containing copies of the economic model in executable format are required with the initial submission.) The Manufacturer should wait until the Submission has been deemed complete by CADTH before submitting the required number of copies in the required format to CADTH as described in section 4.1.4.
- When filing Category 2 Submission Requirements, the Manufacturer should deliver one complete copy to CADTH in electronic format (CD, DVD, or memory stick), as specified in Appendix 7F.
- When both Category 1 and 2 Submission Requirements have been deemed complete, the Manufacturer should provide copies to the participating Drug Plans as described in Appendix 1.

4.1.4 Screening of Submission for Completeness; Required Number of Copies

- An initial screening of the Submission is conducted by CADTH within five (5) days of receipt to ensure that it is complete. CADTH verifies whether the Submission is complete in accordance with the *Common Drug Review Submission Guidelines for Manufacturers*.
- If the Submission is incomplete, CADTH sends a notice to the Manufacturer advising what information is needed to complete the Submission.
- When the Category 1 requirements in the Manufacturer's Submission are deemed complete, CADTH sends an acknowledgement to the Manufacturer and advises the participating Drug Plans. Upon receipt of the acknowledgement, the Manufacturer must ensure that CADTH is provided with:
  - five (5) additional (for a total of six [6]) complete copies of the Category 1 Submission Requirements in electronic format on CD, DVD, or memory stick as specified in Appendix 7F. (CADTH may request additional copies if required.)
  - for a Submission for New Drugs or Drugs with New Indications:
    - five (5) hard copies of section 4.2.1 (f) *Efficacy, Effectiveness, and Safety Evidence,* and section 4.2.1 (g) *Economic and Epidemiologic Information;* OR
  - for a Pre-NOC Submission: :
    - five (5) hard copies of section 4.3.1 (g) *Efficacy, Effectiveness, and Safety Evidence,* and section 4.3.1 (h) *Economic and Epidemiologic Information;* OR
  - for a Submission for New Combination Products (Funded Components):
    - five (5) hard copies of section 4.4.1 (f) *Efficacy, Effectiveness, and Safety Evidence,* and section 4.4.1 (g) *Economic and Epidemiologic Information.*

  (Note: Only one (1) complete set of the Category 2 Submission Requirements is required by CADTH in electronic format on CD, DVD, or memory stick. No additional copies are required by CADTH after the Category 2 requirements have been deemed complete.)
- When both Category 1 and Category 2 requirements have been deemed complete, CADTH sends an acknowledgement to the Manufacturer and advises the participating Drug Plans. Upon receipt of the acknowledgement, the Manufacturer must ensure:
  - that each Drug Plan is provided with one or more copies of the Submission, or part of it, as directed by the Drug Plans (see Appendix 1).

4.1.5 Order of Review

- Submissions (including Pre-NOC Submissions), Resubmissions and Requests for Advice are accepted on an ongoing basis. CADTH publishes, on the CADTH website, targeted CDEC meeting dates when Submissions and Resubmissions may be considered if they are received by a given date. In certain circumstances, CADTH may need to schedule the placement of a Submission or Resubmission on a CDEC meeting agenda other than the posted targeted CDEC meeting date (e.g., when more than three [3] Submissions and Resubmissions have been filed for the same targeted CDEC meeting date).
- Submissions, Resubmissions and Requests for Advice are logged when they are received, so that there is a record of the date of receipt. An acknowledgement of receipt is issued. The date of receipt is considered day zero (0) for the purpose of calculating targeted time frames for reviewing the Submission or Resubmission, and the targeted time frames are posted on the CADTH website.
- Only complete Submissions and Resubmissions, satisfying all of the Submission or Resubmission Requirements, are entered in the review queue.
- Submissions, Resubmissions and Requests for Advice are generally reviewed in the order received, that is, on a "first-come, first-served" basis. However, Submissions or Resubmissions that are granted Post-NOC Priority Review status are given priority when they are targeting the same CDEC meeting as other Submissions or Resubmissions. All applications made to CADTH under the CDR process (i.e., Submissions, Requests for Reconsideration, Requests for Advice, and Resubmissions) are assigned to a tiered queue for review and placement on the CDEC agenda by CADTH staff and the CDEC Chair and participating Drug Plans, as required, pursuant to the following order:
  - Submissions or Resubmissions granted a Post-NOC Priority Review status
  - Reconsiderations, Drug Plan Requests for Clarification, and Resubmissions based on a Reduced Price during the Embargo Period
  - Regular Submissions for New Drugs, Pre-NOC Submissions, New Combination Products containing a New Active Substance, and Drugs with New Indications
  - FWG or Drug Plan-initiated drug-related reviews or Requests for Advice
  - New Combination Products containing existing Drugs or New Drugs that are structurally very similar to existing drugs and that largely duplicate the action of the existing drugs, including Combination Products (Funded Components)
  - Resubmissions.

4.1.6 Tracking

CADTH posts the targeted time frames for the review and the status of the review of all Submissions (including Pre-NOC Submissions and Post-NOC Priority Review Submissions or Resubmissions), Resubmissions, and Requests for Advice on the CADTH website. CADTH updates the website weekly.

4.1.7 Post-NOC Priority Review

- Manufacturers may request Post-NOC Priority Review status in writing when they file a Submission or Resubmission. Manufacturers must provide justification supporting the request.
- Submissions or Resubmission may be granted Post-NOC Priority Review status if:
  - the New Drug or Drug with a New Indication is effective for the treatment of an immediately life-threatening disease or other serious disease for which it offers substantial improvements in clinically important outcome measures of effectiveness, safety, tolerability, and/or quality

of life compared with other available therapies in Canada, or for which no comparable Drug is marketed in Canada; or

- the New Drug or a Drug with a New Indication will have a significant impact in reducing the Drug Plan expenditures for that indication. If listed, the projected total combined savings to the participating Drug Plans must be an average of at least $2.5 million per year for the first three years the product is marketed in Canada.

(Note: *A Drug that qualifies for a Priority Review under Health Canada provisions must meet CDR Post-NOC Priority Review criteria to be eligible for a CDR Post-NOC Priority Review.)*

- Submissions or Resubmissions designated for Post-NOC Priority Review will be placed ahead of other Submissions or Resubmissions in the review queue and are given a preferred status on the CDEC agenda.
- Submissions or Resubmissions that do not meet Post-NOC Priority Review criteria are scheduled as per the tiered queue for review and for the CDEC agenda (section 4.1.5).
- Post-NOC Priority Review status is determined by CADTH staff in consultation with the CDEC Chair, clinical experts, and participating Drug Plans as required.
- If a Manufacturer requests a Priority Review of a Submission or Resubmission based on cost savings, BIAs for the Drug Plans, named in section 4.2.1 (g), Economic and Epidemiologic Information, must be provided when the initial Submission or Resubmission is filed to inform the impact of the New Drug on drug expenditures.
- CADTH advises Manufacturers whether a Post-NOC Priority Review has been granted.
- Submissions or Resubmissions granted Post-NOC Priority Review status must undergo all of the steps in the review process and generally follow the estimated CDR review time frames.
- If the Manufacturer has been granted a Post-NOC Priority Review, CADTH will advise the Manufacturer whether there is an opportunity to place the Submission or Resubmission on an earlier CDEC meeting agenda. CADTH will make this determination and offer this option in those instances where a reduction of eight (8) Business Days in the CDR process may allow the submission to be placed on an earlier CDEC agenda. For this to happen, the Manufacturer must choose to provide comments on the CDR Reviewers' Reports within three (3) Business Days on no more than three (3) pages. CDR Reviewer time to respond to Manufacturer's Comments would be correspondingly reduced to three (3) Business Days. This would decrease the total CDR review process by eight (8) Business Days. Manufacturers must confirm in writing that they have selected the shortened time frames at the time they are advised that a Priority Review has been granted. See the *Procedure for Common Drug Review* (sections 1.1.5 and 7.2).

4.1.8 Copyright Permissions

The Manufacturer is responsible for ensuring that the copyright permission allows for sufficient copies of articles, included in the Submission or Resubmission, to be shared amongst the Review Team and CDEC for the review of the Submission or Resubmission.

4.1.9 Inquiries

All general inquiries, including clarification of Submission Requirements and the Drug review processes, should be directed as indicated in the Inquiries section on page iii.

All inquiries regarding a Submission or Resubmission under review should be directed to the CADTH staff member, whose name is provided to the Manufacturer by CADTH.

Drug Plan-specific inquiries should continue to be directed to the Drug Plan contacts.

4.1.10 Communications and Conflicts of Interest

Once a Submission, Resubmission, or Request for Advice is filed under the CDR process, CADTH will not participate in any meetings, including pre-Submission meetings, with Manufacturers about the Drug under review. Only communications to facilitate the review of the Submission, Resubmission, or Request for Advice as described in the *Procedure for CDR* and these *CDR Submission Guidelines for Manufacturers* will be allowed. This is to avoid any appearance of bias or unfairness.

Direct contact between a Manufacturer and CDEC Members, in their capacity as members of the committee, or CDR Reviewers is not permitted during the Submission review process. Direct approaches in any form to CDEC Members or CDR Reviewers may be viewed as introducing conflict of interest and may create an appearance of bias or unfairness. Direct contact by a Manufacturer of a CDEC Member or CDR Reviewer may result in a significant delay in the Submission review process because additional steps may be required to obtain an unbiased Recommendation on the product.

The identities of CDEC Members are in the public domain. The identities of Reviewers are not revealed; however, the composition of the Review Team is included in the CDR Reports.

4.1.11 Confidentiality

CADTH has developed guidelines to protect Confidential Information obtained for the CDR. The Confidentiality Guidelines are found in Appendix 5. These guidelines ensure that appropriate steps and procedures are in place to protect Confidential Information and to ensure that this information is handled in a consistent manner. CADTH complies with these guidelines when handling information as part of the CDR process. A Manufacturer is deemed to have consented to the guidelines when it files a Submission or Resubmission, or supplies other information to CADTH. A Manufacturer will maintain the confidentiality of documents shared with the Manufacturer by CADTH that are labelled as "confidential." The guidelines constitute an agreement between CADTH and the Manufacturer.

4.2 Submission Requirements for New Drugs, New Combination Products, and Drugs with New Indications

(Note: Requirements for Pre-NOC Submissions are described in section 4.3 and for Combination Products (Funded Components) in section 4.4.)

Submissions for Drugs with New Indication(s) are to contain clinical and pharmacoeconomic information relating to the New Indication(s) only.

The Submission Requirements are grouped into Category 1, Category 2, and Additional Information.

- **Category 1** information must all be included when the Submission is filed and deemed complete in order for the review to proceed.
- **Category 2** information must be provided as a single package in electronic format on a CD, DVD, or memory stick at least twenty (20) Business Days prior to the targeted CDEC meeting at which the Submission will be considered. Category 2 requirements must be satisfied before the Drug review is placed on the CDEC agenda. The Category 2 requirements may be submitted concurrently with Category 1 requirements.
- **Additional Information** includes information that CADTH requires for completion of the review. CADTH may request Additional Information from Health Canada or the Manufacturer. The Manufacturer also has the responsibility of advising CADTH regarding any harms or safety issues that may arise during the time that the Submission is under review and of any communiqués (e.g., "Dear Doctor" letters) being prepared to alert health care professionals about safety concerns. Failure to advise CADTH of these issues as soon as they arise may result in CADTH readjusting and extending the usual CDR timelines in order to review this information.

To expedite the screening of Submissions for completeness and to facilitate the efficient use of documents, Manufacturers must organize the information in the order prescribed (sections 4.2.1 and 4.2.2) and clearly tab it (Appendix 6). The Submission Checklist used by the CADTH can be found in Appendix 7A and the specifications for filing Submissions in electronic format can be found in Appendix 7F.

4.2.1 Category 1 Requirements

One copy of all Category 1 requirements must be submitted to CADTH (see Section 4.1.3 of this document). When deemed complete, the Manufacturer and Drug Plans are apprised (see section 4.1.4 of this document) and steps to initiate the CDR review commence. Category 1 requirements include:

a) Signed Cover Letter

A signed cover letter (an electronic signature is acceptable) from the Applicant, confirming that all the required information has been provided in each copy of the Submission. It should also indicate:

- whether the Submission includes Category 1, Category 2, or both Category 1 and 2 requirements
- whether the electronic versions (CD, DVD, or memory stick) of the Submission are included with the hard copy or being sent separately
- notification when a Priority Review is being requested for the product and justification for the request
- the New Indication when filing a Submission for a Drug with New Indication

- justification for not providing a BIA for any of the ten (10) participating Drug Plans, listed in section 4.2.1(g), Economic and Epidemiologic Information
- a statement confirming that the submitted price is the current marketed price or the Confidential Price that may become effective following the release of the CDEC Final Recommendation (section 4.2.1 [h]).
- the names of the primary and backup contact(s) that CADTH can contact regarding the Submission. [*Note: 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.

b) Table of Contents

A list of the contents and the page numbers on which they are found.

c) Executive Summary

A high-level summary of the Submission, including: a brief description of the Drug and its place in therapy, whether the Drug has received a NOC or NOC/c, a summary of the clinical and pharmacoeconomic evidence (including the unit cost), requested listing criteria, and the rationale (five pages maximum). When a Manufacturer has specified a restricted listing Recommendation (e.g., for a specific population), supporting references should be clearly identified in the Executive Summary.

d) Health Canada NOC or NOC/c

A copy, dated and signed by Health Canada. The NOC or NOC/c must be for the indication for which the Drug is under review. If the Drug in the Submission has received an NOC/c, 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.

e) Product Monograph

The Product Monograph must include the date it was approved by Health Canada, and the company and product names that correspond to the NOC.

f) Efficacy, Effectiveness, and Safety Evidence

The following are required:

- a copy of the Clinical Overview (Module 2.5) and Clinical Summary (Modules 2.7.1, 2.7.3, 2.7.4, and 2.7.6) from Module 2 of the Common Technical Document in hard and electronic format (Microsoft Word or searchable PDF format on CD). (Note: module 2.7.6 must include a tabular listing of studies as well as the individual study synopses.); **OR**
- a copy of the Clinical Studies section of the Comprehensive Summaries or equivalent documentation accepted by Health Canada (as described in Health Canada's New Drug Submission Guideline) in hard and electronic format (Microsoft Word format on CD) if the Submission is not filed with Health Canada in the Common Technical Document format; and
- Copies of published and unpublished studies that address key clinical issues (double blind, randomized controlled trials are given most weight; head-to-head comparison clinical trials between the proposed product and principal comparators are of particular interest). *Note: Phase 1 studies and letters from clinicians should be omitted.*
  It is preferred that unpublished data are submitted in manuscript format; however, if unavailable in manuscript format, the following information should be included in clearly labelled sections:
  - Objective and rationale of study
  - Interventions
  - Study population (including eligibility criteria, baseline characteristics, and sample size)

  - Methods (including randomization method, blinding method, handling of withdrawals and drop-outs, allocation concealment, and outcome measurement)
  - Information about pre-planned extension of trial (if relevant)
  - Results (all beneficial and harmful patient effects, including an itemization of fatal and non-fatal serious adverse events; number of withdrawals and drop-outs with reasons; and measures of dispersion, such as standard deviation or standard error, must be provided for continuous outcomes; numerators and denominators must be provided for dichotomous outcomes)
  - Data analysis
  - Conclusions
- Diagrams following the CONSORT reporting standards or similar diagrams that document the flow of patients through the trials, identified as pivotal trials in Health Canada documentation. (Appendix 8 contains an example of the format and type of required information.) All information in the sections of the sample diagram is to be provided, including reasons for discontinuation and loss to follow-up at each stage of the study. If applicable, the following are to be incorporated into the CONSORT or similar diagram:
  - Additional phases of the study (e.g., screening, washout, baseline, treatment, follow-up) and reasons for discontinuing between phases;
  - Assessments at different time points and reasons for discontinuing between time points; and
  - Analysis populations for each outcome if they differ (primary outcome, key secondary outcomes, harms) and reasons why patients were excluded from each outcome analysis.
- Copies of editorial articles and errata relating to published studies included in the Submission (Note: If none are available, a statement confirming this should be provided.)
- Copies of new data, generated since the last date that data were reported in the studies included in the Health Canada Submission. (Typically, the studies submitted to the 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 resulting after the study has been submitted to Health Canada is required.) These data will be accepted in a variety of formats, including late draft, Clinical Study Report, synopsis, abstract, or conference proceedings. (Note: If none are available, a statement confirming this should be provided.)
- Copies of references supporting the validity of primary outcome measures in studies (if available). If no references are provided, a statement is required to confirm that a search has been undertaken but no references have been located.
- A tabulated list of Canadian and international published and unpublished clinical trials in hard copy and in Microsoft Word format. (See Appendix 9 table template. The template can be downloaded from the CADTH website at www.cadth.ca. All parts of the template must be completed as per instructions in footnotes below the table.)
  - A list of all completed published studies, including editorial articles and errata relating to them, and unpublished studies included in the Submission and where they are located in the Submission, including the section in the Submission and the Submission page number, and, when available, a PDF copy of the abstract or publication should be inserted in the table. *(Note: All Phase 3 studies, described in the Common Technical Document, are to be listed.)*
  - A list of all completed published and unpublished studies not included in the Submission (*Note: For Drugs available for 10 years or more in Canada or internationally, CADTH should be contacted for guidance on what to include in the table*.)
  - A list of all ongoing studies for all indications.

Upon review of the information in the table, CADTH may request more details or copies of the studies.

- 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 trials have been disclosed (Appendix 10 letter template). The template may be downloaded from the CADTH website at www.cadth.ca. If CADTH discovers undisclosed unpublished trials through other sources, this will result in the Submission being place on a later CDEC meeting agenda to allow time for the retrieval and review of the trials.

g) Economic and Epidemiologic Information

The following are required:

- An appropriate pharmacoeconomic evaluation for the full population identified in the approved Health Canada indication. If there are subgroups that may benefit from the Drug or specific reimbursement criteria requested by the Manufacturer, additional analyses should be provided. Refer to Appendix 15 for guidance on the type of economic analyses and what to submit. Please also refer to the CADTH document *Guidelines for the Economic Evaluation of Health Technologies: Canada.*
- Three (3) CDs containing copies of the economic model in executable format provided only in the Manufacturer's initial Submission sent for assessment of completeness. No additional copies are required by CADTH once the Submission is deemed complete. (Note: Copies of the economic model are not required in the Submissions sent to the participating Drug Plans.)
- The economic model must meet the following characteristics:
  - The submitted model is the basis for the economic evaluation
  - The economic model must be in an unlocked (or executable) format, i.e., full access to the programming code is required and running of the model should be unhindered.
  - The economic model must be in one of the following formats: Excel, TreeAge / DATA, or Arena.
  - Documentation detailing the methods used in the modeling exercise and basic user information must be included.

  Note: Manufacturers are asked to contact CADTH in advance when they are using specialized programs to ensure that they meet CADTH's requirements and to receive direction on how the model and software should be provided in the Submission. Manufacturers are expected to provide CADTH with the necessary requirements to run the model (i.e., licences, laptop with model, and software), which will be returned to the Manufacturer at the end of the review process at the Manufacturer's expense.

  The CDR Reviewer must be able to vary individual parameters, view the calculations, and run the model to generate results. If statistical analyses of data sets are included in the model, the Manufacturer should provide a description of the data sources and analyses conducted, and results from the analyses. The type of information that CDR requires for its examination of the model and the preferred format for receiving it are described in Table 1.

Table 1: CDR Pharmacoeconomic Information Requirements	
Information Elements	**Format**
Basis for the pharmacoeconomic study (model, spreadsheet)	A model* (or a spreadsheet) that is unlocked (or executable). The user should be able to specify inputs, view calculations, and run various analyses.
Media	CD-ROM or laptop
Software requirements	The Manufacturer must describe the software and system requirements to run the model. The submitted model must be in one of the following formats: Excel, TreeAge / DATA, or Arena. Where Manufacturers are using specialized programs, they are asked to contact CADTH in advance to ensure that the programs meet CADTH's requirements and to receive direction on how the model and software should be provided in the Submission. Manufacturers are expected to provide CADTH with the necessary requirements to run the model (i.e., licences, laptop with model, and software), which will be returned to the Manufacturer at the end of the review process at the Manufacturer's expense.
Basic user guide to the model	Hard copy and electronic format
Model documentation (manuscripts or a summary of the model report may be submitted)	Hard copy and electronic format
Description of the statistical analyses included in the model (data sources, methods, and results)	Hard copy and electronic format

** Note: The model will be examined by internal and external CDR Reviewers. The model will not be released to any third parties.*

- Number of patients accessing the New Drug, pre-NOC, and post-NOC up to the time of the Submission, either as compassionate supply from the Manufacturer, under the Special Access Program, or as part of a clinical trial. This information must be provided as a Category 1, as well as a Category 2 requirement, as background for the BIAs.
- Disease prevalence — the prevalence or incidence of the disease(s) or condition(s) for which the Drug is approved by Health Canada — should be provided for the Canadian population, with a breakdown by participating province, territory, and First Nations' populations where available (must be referenced). This information must be provided as a Category 1 and also as a Category 2 requirement as background for the BIAs.
- BIAs must be provided as a Category 1 requirement, if a Post-NOC Priority Review based on cost savings is requested, for each of the following Drug Plans, in accordance with their requirements: Newfoundland and Labrador, Prince Edward Island, Nova Scotia, New Brunswick, Ontario, Manitoba, Saskatchewan, Alberta, British Columbia, and Non-Insured Health Benefits Program (waivers may be granted upon submission of appropriate justification). 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 supporting documentation is required:
  - all supporting information used in BIAs, such as market research information or utilization reports
  - copies of documents cited in the BIAs
  - budget impact model (Excel spreadsheet), showing how the national cost savings is derived
  - an explanation of the national BIA and the assumptions on which it is based.

h) Pricing and Availability Information

- Submitted prices, reported as price per smallest unit to four decimal places and per smallest dispensable unit for all dosage forms, strengths, and package sizes. (*Note: The submitted price is the price that is effective for all participating Drug Plans. It can be the current market price in Canada, or the Confidential Price that may become effective for all participating 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.)*
  - If the submitted price is a Confidential Price that may become effective following release of the CDEC Final Recommendation, the Manufacturer must provide a signed commitment to honour this price for all participating Drug Plans (Appendix 11 letter template).
  - Should issues arise regarding the submitted price, the participating Drug Plans may consider next steps, including the option of submitting a Request for Advice to CDEC about its Final Recommendation considering the publicly available current market price. This could potentially result in a changed Final Recommendation.
  - Only one current or Confidential Price per unit is to be submitted per Drug that is under current CDR review (i.e., only one price for all indications undergoing CDR review concurrently).
  - The submitted price must be used in the pharmacoeconomic evaluation and in the BIAs, included in the Submission.
- Method of distribution to pharmacies (wholesale, direct, or other arrangements).

i) Letter Authorizing Unrestricted Sharing of Information

This letter from the holder of the NOC or NOC/c, printed on company letterhead and signed by an appropriate senior official, should permit 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.

(See Appendix 12 letter template. The template may also be downloaded from the CADTH website, www.cadth.ca.)

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.

4.2.2 Category 2 Requirements

One set of Category 2 requirements is to be submitted as electronic files on a CD, DVD, or memory stick, as specified in Appendix 7F. No hard copies or additional electronic copies are required by CADTH. All Category 2 information must be provided as a single package to CADTH at least twenty (20) Business Days prior to the targeted CDEC meeting at which the Submission will be considered. Category 2 requirements must be satisfied before the Drug review is placed on the CDEC agenda. Category 2 requirements may be submitted concurrently with Category 1 requirements. When advised that Category 1 and 2 requirements are deemed complete, Manufacturers should provide the Drug Plans with copies of the Submission as described in Appendix 1. Category 2 requirements include:

a) Letter Confirming Ability to Supply

A letter providing assurance of a Manufacturer's ability to meet the anticipated demand for the product at the time of filing the Submission. (See Appendix 11 letter template. The template may also be downloaded from the CADTH website, www.cadth.ca.)

b) Drug Notification Form

A completed, dated, and signed copy (also known as the Drug Identification Number [DIN] notification form) for all strengths and dosage forms.

c) Certified Product Information Document

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

d) Product Patent Expiration Date

e) Compendium of Pharmaceuticals and Specialties listing

A letter indicating the current or intended inclusion of the product monograph in the Compendium of Pharmaceuticals and Specialties (CPS).

f) Pharmaceutical Advertising Advisory Board (PAAB)-approved promotional materials — or a draft copy of material submitted to PAAB

If a Manufacturer does not intend to produce and use promotional material for the product, the Manufacturer may request that this requirement be waived. A letter, signed by a senior company official, stating the rationale and period of time (month and year) for which no promotional material will be used, must be provided.

g) Economic and Epidemiologic Information

- Number of patients accessing the New Drug, pre-NOC, and post-NOC up to the time of the Submission, either as compassionate supply from the Manufacturer, under the Special Access Program, or as part of a clinical trial. This information must be provided as a Category 1 and a Category 2 requirement.
- Disease prevalence — the prevalence/incidence of the disease(s)/condition(s) for which the Drug is approved by Health Canada — should be provided for the Canadian population, with a breakdown by participating province, territory, and First Nations' population where available (must be referenced). This information must be provided as a Category 1 and a Category 2 requirement.
- BIAs — if not already filed with Request for Priority Review based on cost savings — for each of the following Drug Plans, in accordance with their requirements: Newfoundland and Labrador, Prince Edward Island, Nova Scotia, New Brunswick, Ontario, Manitoba, Saskatchewan, Alberta, British Columbia, and Non-Insured Health Benefits Program (waivers may be granted upon submission of appropriate justification). 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 supporting documentation is required:
  - all supporting information used in BIAs, such as market research information or utilization reports
  - copies of documents cited in the BIAs.

4.2.3 Additional Information

The following information may be requested by CADTH:

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 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 the Health Canada Reviewers' Report for each Submission. To avoid delays in providing the report to CADTH, Manufacturers are encouraged to request the report from Health Canada as soon as they are assured that a NOC or NOC/c will be issued and to forward it immediately to CADTH upon receipt. CADTH has not included the Health Canada Reviewers' Report as a Category 1 requirement in recognition that this report is not immediately available from Health Canada at the time that the NOC or NOC/c is issued but that Manufacturers often file Submissions with CADTH soon after receipt of a NOC or NOC/c.

c) Periodic Safety Update Reports

CADTH may request Periodic Safety Update Reports (PSURs) from the Manufacturer.

d) Clinical Study Report

CADTH may request the Clinical Study Report, or parts of it, in searchable electronic format (Microsoft Word or searchable PDF on CD, DVD, or memory stick).

4.3 Pre-NOC Submission Requirements

A Pre-NOC Submission is for a New Drug or a Drug with a New Indication for which Health Canada is highly likely to issue an NOC or NOC/c within ninety (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 the time of filing; however, they are to be provided as soon as they are 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 NOC/c will be issued on a particular date, or at all, Manufacturers may consider filing a Submission with CADTH up to ninety (90) calendar days in advance of anticipated NOC or NOC/c if no significant issues have been raised by Health Canada.

Although most of the Pre-NOC Submission Requirements are the same as those for other Submissions, there are some variations, and thus the Pre-NOC Submission Requirements are presented separately in this section.

The Submission Requirements are grouped into Category 1, Category 2, and Additional Information.

- **Category 1** information must all be included when the Submission is filed in order for the review to proceed.
- **Category 2** information must be provided as a single package within twenty (20) Business Days of receiving a NOC.

- **Additional Information** includes information CADTH requires for completion of the review. CADTH may request additional information from Health Canada or the Manufacturer. The Manufacturer also has the responsibility of advising CADTH regarding any harms or 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 as soon as they arise may result in CADTH readjusting and extending the usual CDR timelines in order to review this information.

To expedite the screening of Pre-NOC Submissions for completeness and to facilitate the efficient use of documents, Manufacturers must organize the information in the order prescribed (sections 4.3.1 and 4.3.2) and clearly tab it (Appendix 6). A copy of the Pre-NOC Submission Checklist used by the CDR Directorate is included for reference (Appendix 7B) and the specifications for filing Pre-NOC Submissions in electronic format can be found in Appendix 7F.

4.3.1 Category 1 Pre-NOC Submission Requirements

(Note: It is the responsibility of the Manufacturer to advise Health Canada of the intent to file a Pre-NOC Submission with CADTH.)

One copy of all Category 1 requirements must be submitted to CADTH as described in section 4.1.3.. When deemed complete, the Manufacturer and Drug Plans are apprised (see section 4.1.4 of this document). The CDR review is initiated when the Submission Requirements are complete.) The Manufacturers should provide the Drug Plans with copies of the Pre-NOC Submission as described in Appendix 1 when advised that Category 1 and 2 requirements are deemed complete.

Category 1 requirements include:

a) Signed Cover Letter

A signed cover letter (an electronic signature is acceptable) from the Manufacturer, confirming that all the required information has been provided in each copy of the Submission. It should also include:

- A clear description of the Submission being filed (i.e., Category 1 requirements for Pre-NOC Submission);
- Whether the electronic versions (CD, DVD, or memory stick) of the Submission are included with the hard copy or being sent separately;
- Intention to provide Category 2 requirements within twenty (20) business days of receiving a NOC or NOC/c;
- Justification for not providing a BIA for any of the ten (10) participating Drug Plans listed in section 4.3.1 (h), Economic and Epidemiologic Information;
- Statement confirming that the submitted price is the current marketed price or the Confidential Price that may become effective following the release of the CDEC Final Recommendation (section 4.3.1 [i]);
- The names of the primary and backup contact(s) that CADTH can contact regarding the Submission. (Note: 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.

b) Table of Contents

A list of the contents and the page numbers on which they are found.

c) 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.

d) Executive Summary

A high-level summary of the Submission, including a brief description of the Drug and its place in therapy, a summary of the clinical and pharmacoeconomic evidence (including the unit cost), requested listing criteria, and the rationale (five pages maximum. When a Manufacturer has specified restricted criteria for a listing recommendation (e.g., for a specific population), supporting information (e.g., references, trial data) should be clearly identified in the Executive Summary.

e) Health Canada NOC or NOC/c

A target date for receipt of a NOC or NOC/c. A copy of the NOC or NOC/c, dated and signed by Health Canada, is to be provided by email as soon as it is available (i.e., on the day received from Health Canada) and along with confirmation that all information filed with CADTH for this Submission is complete (See Appendix 13 for letter template). If the Drug in the Submission has received an NOC/c, 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

A *draft Product Monograph* to CADTH at the time of filing a Submission.

- The draft Product Monograph must show the company and product names that correspond to the NOC.
- Following the Product Monograph meeting, the revised version (with track changes visible and a clean copy) of the Product Monograph is to be provided to CADTH by email as soon as possible.

The *Health Canada-approved Final Product Monograph* (showing the date it was approved by Health Canada) and the company and product names that correspond to the NOC or NOC/c.

- A hard copy and an electronic copy (Microsoft Word format on CD) of the Health Canada approved Final Product Monograph are required as soon as available.

g) Efficacy, Effectiveness, and Safety Evidence

The following are required:

- A copy of the Clinical Overview (Module 2.5) and Clinical Summary (Modules 2.7.1, 2.7.3, 2.7.4, and 2.7.6) from Module 2 of the common Technical Document in hard and electronic format (Microsoft Word or searchable PDF format on CD). (Note: module 2.7.6 must include a tabular listing of studies as well as the individual study synopses.)
- Copies of published and unpublished studies that address key clinical issues (double blind, randomized controlled trials are given most weight; head-to-head comparison clinical trials between the proposed product and principal comparators are of particular interest. (Note: Phase 1 studies and letters from clinicians should be omitted.)
- Unpublished data, preferably submitted in manuscript format; however, if unavailable in manuscript format, the following information should be included in clearly labelled sections:
  - Objective and rationale of study
  - Interventions
  - Study population (including eligibility criteria, baseline characteristics, and sample size 0
  - Methods (including randomization method, blinding method, handling of withdrawals and drop-outs, allocation concealment, and outcome measurement)

  - Information about pre-planned extension of trial (if relevant)
  - Results (all beneficial and harmful patient effects, including and itemization of fatal and non-fatal serious adverse event; number of withdrawals and drop-outs with reasons; measure of dispersion, such as standard deviation or standard error, must be provided for continuous outcomes; numerators and denominators must be provided for dichotomous outcomes)
  - Data analysis
  - Conclusions.
- Diagrams following the CONSORT reporting standards or similar diagrams that document the flow of patients through the trials, identified as pivotal trials in Health Canada documentation. (Appendix 8 contains an example of the format and type of required information.) All information in the sections of the sample diagram is to be provided, including reasons for discontinuation and loss to follow-up at each stage of the study. If applicable, the following are to be incorporated into the CONSORT or similar diagram:
  - Additional phases of the study (e.g., screening, washout, baseline, treatment, follow-up) and reasons for discontinuing between phases;
  - Assessments at different time points and reasons for discontinuing between time points; and
  - Analysis populations for each outcome if they differ (primary outcome, key secondary outcomes, harms) and reasons why patients were excluded from each outcome analysis.
- Copies of editorial articles and errata, relating to the published studies included in the Submission (Note: If none are available, a statement confirming this should be provided.)
- Copies of new data, generated since the last date that data were reported in the studies included in the Health Canada Submission. (Typically, the studies submitted to CADTH are the same as those submitted to Health Canada. The data resulting after the study has been submitted to Health Canada is required.) (Note: If none are available, a statement confirming this should be provided.)
- Copies of reference supporting the validity of outcome measures in studies (if available). If no references are provided, a statement is required to confirm that a search has been undertaken but no references have been located.
- A tabulated list of Canadian and international published and unpublished clinical trials in hard copy and in Microsoft Word format. (See Appendix 9 table template. The template can be downloaded from the CADTH website at www.cadth.ca.) (Note: All parts of the template must be completed as per instructions in footnotes below the table.)
  - A list of all completed published studies, including editorial articles and errata relating to them, and unpublished studies included in the Submission and where they are located in the Submission, including the section in the Submission and the Submission page number, and, when available, a PDF copy of the abstract or publication should be inserted in the table. (Note: All Phase 3 studies, described in the Common Technical Document, are to be listed.)
  - A list of all completed published and unpublished studies not included in the Submission. (Note: For Drugs available for 10 years or more in Canada or internationally, CADTH should be contacted for guidance on what to include in the table.)
  - A list of all ongoing studies for all indications.
    Upon review of the information in the table, CADTH may request more details or copies of the studies.
- 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 trials have been disclosed (Appendix 10 letter template). The template may be downloaded from the CADTH website at www.cadth.ca. If CADTH discovers undisclosed unpublished trials through other sources, this will result in the Submission being place on a later CDEC meeting to allow time for the review of the unpublished trials.

h) Economic and Epidemiologic Information

The following are required:

- An appropriate pharmacoeconomic evaluation is required for the full population identified in the approved Health Canada indication. If there are subgroups that may benefit from the Drug or specific reimbursement criteria requested by the Manufacturer, additional analyses should be provided. Refer to Appendix 15 for guidance on the type of economic analyses and what to submit. Please also refer to the CADTH document, *Guideline for the Economic Evaluation of Health Technologies: Canada.*
- Three (3) CDs containing copies of the economic model in executable format provided only in the Manufacturer's initial Submission sent for assessment of completeness. No additional copies are required by CADTH once the Submission is deemed complete. (Note: Copies of the economic model are not required in the Submissions sent to the participating Drug Plans.)
- The economic model must meet the following characteristics:
  - The submitted model is the basis for the economic evaluation.
  - The economic model must be in an unlocked (or executable) format; i.e., full access to the programming code is required and running of the model should be unhindered.
  - The economic model must be in one of the following formats: Excel, TreeAge / DATA, or Arena.
  - Documentation detailing the methods used in the modelling exercise and basic user information must be included.

  Note: Manufacturers are asked to contact CADTH in advance when they are using specialized programs to ensure that they meet CADTH's requirements and to receive direction on how the model and software should be provided in the Submission. Manufacturers are expected to provide CADTH with the necessary requirements to run the model (i.e., licences, laptop with model, and software), which will be returned to the Manufacturer at the end of the review process at the Manufacturer's expense.

  The CDR Reviewer must be able to vary individual parameters, view the calculations, and run the model to generate results. If statistical analyses of data sets are included in the model, the Manufacturer should provide a description of the data sources and analyses conducted, and results from the analyses. The type of information that CDR requires for its examination of the model and the preferred format for receiving it are described in Table 1.

Table 1: CDR Pharmacoeconomic Information Requirements	
Information Elements	**Format**
Basis for the pharmacoeconomic study (model, spreadsheet)	A model* (or a spreadsheet) that is unlocked (or executable). The user should be able to specify inputs, view calculations, and run various analyses.
Media	CD-ROM or laptop
Software requirements	The Manufacturer must describe the software and system requirements to run the model. The submitted model must be in one of the following formats: Excel, TreeAge / DATA, or Arena. Where Manufacturers are using specialized programs, they are asked to contact CADTH in advance to ensure that the programs meet CADTH's requirements and to receive direction on how the model and software should be provided in the Submission. Manufacturers are expected to provide CADTH with the necessary requirements to run the model (i.e., licences, laptop with model, and software), which will be returned to the Manufacturer at the end of the review process at the Manufacturer's expense.
Basic user guide for the model	Hard copy and electronic format
Model documentation (manuscripts or a summary of the model report may be submitted)	Hard copy and electronic format
Description of the statistical analyses included in the model (data sources, methods, and results)	Hard copy and electronic format

*The model will be examined by internal and external CDR reviewers. The model will not be released to any third parties.

- Number of patients accessing the New Drug, pre-NOC, and post-NOC up to the time of the Submission, either as compassionate supply from the Manufacturer, under the Special Access Program, or as part of a clinical trial. This information must be provided as a Category 1 requirement, as well as a Category 2 requirement, as background for the BIAs.
- Disease prevalence — the prevalence or incidence of the disease(s) or condition(s) for which the Drug is approved by Health Canada — should be provided for the Canadian population, with a breakdown by participating province, territory, and First Nations' population where available (must be referenced). This information must be provided as a Category 1 requirement, as well as a Category 2 requirement, as background for the BIAs.

i) Pricing and Availability Information

- Submitted prices, reported as price per smallest unit to four decimal places and per smallest dispensable unit for all dosage forms, strengths and package sizes. *(Note: The submitted price is the price that is effective for all participating Drug Plans. It can be the current market price in Canada or the Confidential Price that may become effective for all participating 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.)*
  - If the submitted price is a Confidential Price that may become effective following release of the CDEC Final Recommendation, the Manufacturer must provide a signed commitment to honor this price for all participating Drug Plans (Appendix 11 letter template).
  - Should issues arise regarding the submitted price, the participating Drug Plans may consider next steps, including the option of submitting a Request for Advice to CDEC about its Final Recommendation considering the publicly available current market price. This could potentially result in a changed Final Recommendation.

  - Only one current or Confidential Price per unit is to be submitted per Drug that is under current CDR review (i.e., only one price for all indications undergoing CDR review concurrently).
  - The submitted price must be used in the pharmacoeconomic evaluation and in the BIAs, included in the Submission.
- Method of distribution to pharmacies (wholesale, direct, or other arrangements).

j) Letter Authorizing Unrestricted Sharing of Information

This letter from the Manufacturer, applying for an NOC or NOC/c, printed on company letterhead and signed by and appropriate senior official, should permit 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
- PMPRB.

(Appendix 12 letter template. The template may also be downloaded from the CADTH website, www.cadth.ca.)

(Note: 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 which may have information regarding the product file with Health Canada.)

k) Letter of Authorization

A Letter of Authorization from the Manufacturer, applying for an NOC or NOC/c, printed on company letterhead and signed by an appropriate senior official, allowing Health Canada to share information with CADTH, accompanied by a form completed by Health Canada listing information to be sent to CADTH (Appendices 14[a] and 14[b]).

l) Table Listing Clarifaxes

A table listing the Clarifaxes and the responses during the Health Canada review of the Drug. The topic for clarification, date, response, and date of response are to be provided.

m) Copies of Clarifaxes

Copies of all Clarifaxes and responses to the point of the NOC or NOC/c being issued by Health Canada.

4.3.2 Category 2 Pre-NOC Submission Requirements

One set of Category 2 requirements is to be submitted as electronic files on a CD, DVD, or memory stick, as specified in Appendix 7F. No hard copies or additional electronic copies are required by CADTH. All Category 2 information must be provided as a single package to CADTH within twenty (20) Business Days of the Manufacturer's receipt of the NOC or NOC/c. When advised that Category 1 and 2 requirements are deemed complete, Manufacturers should provide the Drug Plans with copies of the Submission as described in Appendix 1. Category 2 requirements include:

a) Signed Cover Letter

A signed cover letter (an electronic signature is acceptable) from the Manufacturer, confirming that all the required information has been provided. It should also include:

- a clear description of the Submission being filed (i.e., Category 2 requirements for Pre-NOC Submission);

- the date the NOC or NOC/c was received;
- a description of and supporting documents for information in the Category 1 submission that may have changed since it was filed (e.g., any updated ongoing studies information).

b) Letter Confirming Ability to Supply

A letter providing assurance of a Manufacturer's ability to meet the anticipated demand for the product at the time of filing the Submission. (Appendix 11 letter template.) The template may also be downloaded from the CADTH website, www.cadth.ca)

c) Drug Notification Form

A completed, dated and signed copy (also known as the Drug Identification Number [DIN] notification form) for all strengths and dosage forms.

d) Certified Product Information Document

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

e) Product Patent Expiration Date

f) Compendium of Pharmaceuticals and Specialties listing

A letter indicating the current or intended inclusion of the product monograph in the Compendium of Pharmaceuticals and Specialties (CPS).

g) Pharmaceutical Advertising Advisory Board (PAAB)-approved promotional materials — or a draft copy of material submitted to PAAB

If a Manufacturer does not intend to produce and use promotional material for the product, the Manufacturer may request that this requirement be waived. A letter, signed by a senior company official, stating the rationale and period of time (month and year) for which no promotional material will be used, must be provided.

h) Economic and Epidemiologic Information

- Number of patients accessing the New Drug, pre-NOC, and post-NOC up to the time of the Submission, either as compassionate supply from the Manufacturer, under the Special Access Program, or as part of a clinical trial
- Disease prevalence — the prevalence/incidence of the disease(s)/condition(s) for which the Drug is approved by Health Canada should be provided for the Canadian population, with a breakdown by participating province, territory, and First Nations' population, where available (must be referenced)
- BIAs —for each of the following Drug Plans, in accordance with their requirements: Newfoundland and Labrador, Prince Edward Island, Nova Scotia, New Brunswick, Ontario, Manitoba, Saskatchewan, Alberta, British Columbia, and Non-Insured Health Benefits Program (waivers may be granted upon submission of appropriate justification). 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 supporting documentation is required:
  - all supporting information used in BIAs such as market research information or utilization reports
  - copies of documents cited in the BIAs.

4.3.3 Additional Information

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 communiqués as soon as they arise may result in CADTH readjusting and extending the usual CDR timelines in order to review this information.

Health Canada may also provide CADTH with any information pertinent to the review of the drug at any time during the CDR review process.

b) Health Canada Reviewers' Report

The summary of the assessment of the New Drug Submission by Health Canada reviewers will be provided to CADTH either by Health Canada directly or by the Manufacturer. This will be determined in consultation with CADTH, Health Canada, and the Manufacturer.

c) Periodic Safety Update Reports

CADTH may request PSURs from the Manufacturer.

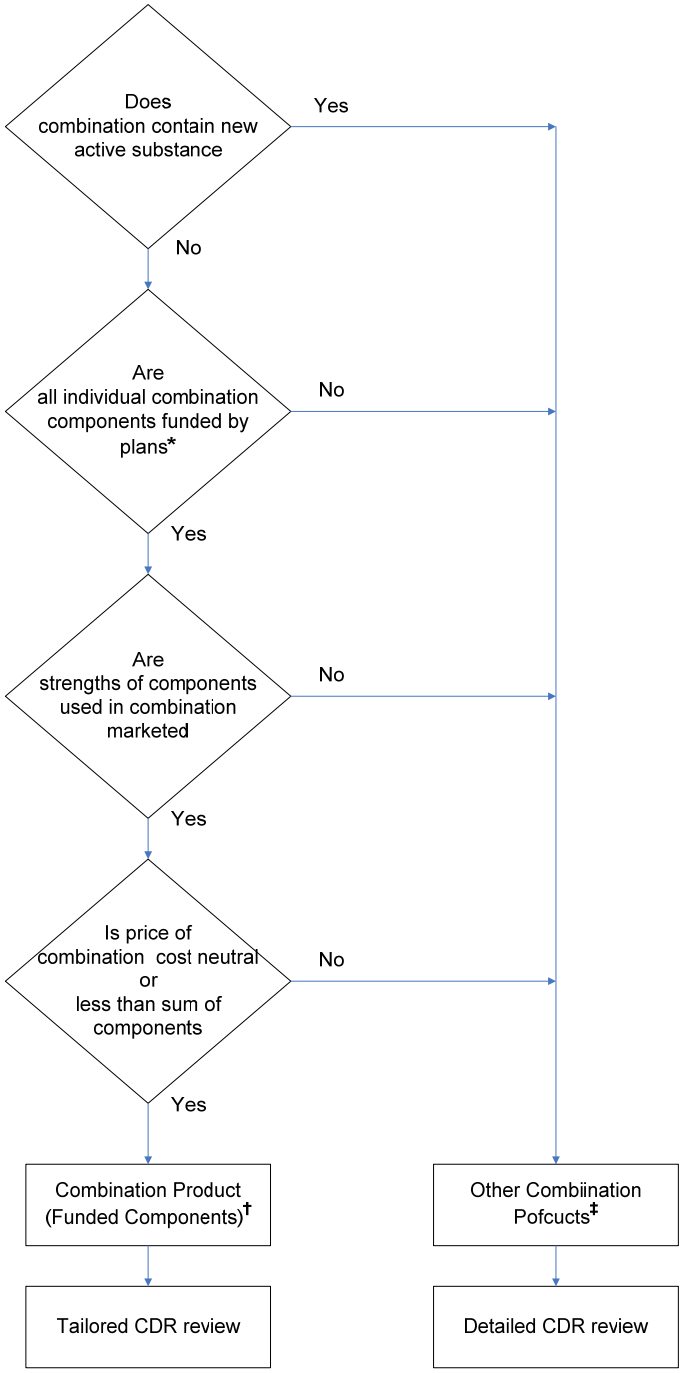
d) Clinical Study Report

CADTH may request the Clinical Study Report, or parts of it, in searchable electronic format (Microsoft Word or searchable PDF on CD).

4.4 Submission Requirements for New Combination Products (Funded Components)

New Combination Products (Funded Components) contain two or more drugs that are already funded by Drug Plans. They may contain funded non-prescription drugs, but at least one component must be a prescription drug. These combination products undergo a tailored review and the Submission Requirements for Combination Products (Funded Components) have been modified to facilitate a tailored review of the Submission. All other Combination Products undergo the regular CDR review and must be submitted in accordance with regular Submission Requirements. Following is a flowchart (Figure 2) to assist in deciding whether a Submission for a New Combination Product should be filed as a Submission for a Combination Product (Funded Components) or a regular Submission:

Figure 2: Flowchart for Determining What Type of Review and Submission is Required for Combination Products



CDR = Common Drug Review

* If there are questions about whether a combination product submission should proceed to CDR or whether it requires a detailed or tailored review, input or direction will be sought from participating Drug Plans.

† Combination Product (Funded Components) = combination product containing two or more drugs already funded by the participating drug plans. The combination product may contain non-prescription drugs funded by the drug plans, but at least one other component must be a prescription drug. Submissions for these types of combinations must meet the modified submission requirements for Combination Products (Funded Components) which have been developed to facilitate a tailored review.

‡ Other Combination Products = all other types of combination products which must meet regular submission requirements.

Following are the Submission Requirements for Combination Products (Funded Components):

- **Category 1** information must all be included when the Submission is filed in order for the review to proceed. (See section 4.1.3.)
- **Category 2** information must be provided as a single package in electronic format on a CD, DVD, or memory stick at least twenty (20) Business Days prior to the targeted CDEC meeting at which the Submission will be considered. Category 2 requirements must be satisfied before the Drug review is placed on the CDEC agenda. The Category 2 requirements may be submitted concurrently with Category 1 requirements.
- **Additional Information** includes information CADTH requires for completion of the review. CADTH may request Additional Information from Health Canada or the Manufacturer. The Manufacturer also has the responsibility of advising CADTH regarding any harms or 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 as soon as they arise may result in CADTH readjusting and extending the usual CDR timelines in order to review this information.

To expedite the screening of Submissions for completeness and to facilitate the efficient use of documents, Manufacturers must organize the information in the order prescribed and clearly tab it. A copy of the Submission Checklist used by CADTH is included in Appendix 7C.

4.4.1 Category 1 Requirements

One copy of all Category 1 requirements must be submitted to CADTH. When deemed complete (see section 4.1.4), the Manufacturer and Drug Plans are apprised and steps to initiate the CDR review commence. Category 1 requirements include:

a) Signed Cover Letter

A signed cover letter (an electronic signature is acceptable) from the Applicant confirming that all the required information has been provided in each copy of the Submission. It should also indicate:

- whether the Submission includes Category 1, Category 2, or both Category 1 and 2 requirements
- whether the electronic versions (CD, DVD, or memory stick) of the Submission are included with the hard copy or being sent separately
- notification that a Priority Review is being requested for the product and justification for the request
- the New Indication when filing a Submission for a Drug with New Indication
- justification for not providing a BIA for any of the ten (10) participating Drug Plans, listed in section 4.4.1(g), Economic and Epidemiologic Information
- statement confirming that the submitted price is the current marketed price or the Confidential Price that may become effective following the release of the CDEC Final Recommendation, section 4.4.1(h).
- the names of the primary and backup contact(s) that CADTH can contact regarding the Submission. (Note: 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.

b) Table of Contents

A list of the contents and the page numbers on which they are found.

c) Executive Summary

A high-level summary of the Submission, including a brief description of the Drug and its place in therapy, a summary of the clinical and pharmacoeconomic evidence (including the unit cost), requested listing criteria, and the rationale (five pages maximum). When a Manufacturer has specified a restricted listing Recommendation (e.g., for a specific population), supporting references should be clearly identified in the Executive Summary.

d) Health Canada NOC or NOC/c

A copy dated and signed by Health Canada. If the Drug in the Submission has received an NOC/c, 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.

e) Product Monograph

The Product Monograph should show the date it was approved by Health Canada and the company and product names that correspond to the NOC.

f) Efficacy, Effectiveness, and Safety Evidence Supporting Evidence for Combination Products (Funded Components)

(Note: A template for submitting the required clinical and economic information for a Combination Product [Funded Components] can be found in Appendix 16 and the CADTH website at www.cadth.ca.)

- A completed template with the following information and references for the information:
  - pharmacologic and therapeutic rationale for the combination
  - evidence of bioequivalence
    - a copy of the Health Canada report demonstrating bioequivalence of the Combination Products with the individual components
    - a verbatim quote from the Health Canada report declaring bioequivalence of the Combination Product with the individual components
    - pharmacokinetic information
  - place in therapy of the combination
  - harms information for combination, components, and comparators
  - cost information.
- One clinical study using the Combination Product (Funded Components) in question (not the individual components) must be supplied. It can be a pharmacokinetic study.

g) Economic and Epidemiologic Information

(Note: The template for submitting a Combination Product [Funded Components] contains cost tables that must be completed. See Appendix 16 and CADTH website at www.cadth.ca.)

- Number of patients accessing the New Drug, pre-NOC, and post-NOC up to the time of the Submission, as compassionate supply from the Manufacturer, under the Special Access Program, or as part of a clinical trial. This information must be provided as a Category 1 requirement, as well as a Category 2 requirement, as background for the BIAs.
- Disease prevalence — the prevalence or incidence of the disease(s) or condition(s) for which the Drug is approved by Health Canada — should be provided for the Canadian population, with a breakdown by participating province, territory, and First Nations' population where available (must be referenced). This information must be provided as a Category 1 requirement, as well as a Category 2 requirement, as background for the BIAs.
- BIAs must be provided as a Category 1 requirement, if a Priority Review based on cost savings is requested , for each of the following Drug Plans in accordance with their requirements:

Newfoundland and Labrador, Prince Edward Island, Nova Scotia, New Brunswick, Ontario, Manitoba, Saskatchewan, Alberta, British Columbia, and Non-Insured Health Benefits Program (waivers may be granted upon submission of appropriate justification). 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 supporting documentation is required:

- copies of documents cited in the BIAs.
- all supporting information used in BIAs such as market research information or utilization reports
- budget impact model (Excel spreadsheet) showing how the national cost savings is derived
- an explanation of the national budget impact analysis and the assumptions on which it is based.

h) Pricing and Availability Information

- Submitted prices, reported as price per smallest unit to four decimal places and per smallest dispensable unit for all dosage forms, strengths, and package sizes.
  Note: The submitted price is the price that is effective for all participating Drug Plans. It can be the current market price in Canada or the Confidential Price that may become effective for all participating 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.
  - If the submitted price is a Confidential Price that may become effective following release of the CDEC Final Recommendation, the Manufacturer must provide a signed commitment to honour this price for all participating Drug Plans (Appendix 11 letter template).
  - Should issues arise regarding the submitted price, the participating Drug Plans may consider next steps, including the option of submitting a Request for Advice to CDEC about its Final Recommendation considering the publicly available current market price. This could potentially result in a changed Final Recommendation.
  - Only one current or Confidential Price per unit is to be submitted per Drug that is under current CDR review (i.e., only one price for all indications undergoing CDR review concurrently).
  - The submitted price must be used in the BIAs that are included in the Submission.
- Method of distribution to pharmacies (wholesale, direct, or other arrangements).

i) Letter Authorizing Unrestricted Sharing of Information

This letter from the holder of the NOC or NOC/c, printed on company letterhead and signed by an appropriate senior official, should permit 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 (PMPRB).

(Appendix 12 letter template. The template may also be downloaded from the CADTH website, www.cadth.ca.)

(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.)

4.4.2 Category 2 Requirements

One set of Category 2 requirements is to be submitted as electronic files on a CD, DVD, or memory stick, as specified in Appendix 7F. No hard copies are required by CADTH. All Category 2 information must be provided as a single package to CADTH at least twenty (20) Business Days prior to the targeted CDEC meeting at which the Submission will be considered. Category 2 requirements must be satisfied before the Drug review is placed on the CDEC agenda. Category 2 requirements may be submitted concurrently with Category 1 requirements. When advised that Category 1 and 2 requirements are deemed complete, Manufacturers should provide the Drug Plans with copies of the Submission as described in Appendix 1. Category 2 requirements include:

a) Letter Confirming Ability to Supply

A letter providing assurance of a Manufacturer's ability to meet the anticipated demand for the product at the time of filing the Submission. (See Appendix 11 letter template. The template may also be downloaded from the CADTH website, www.cadth.ca.)

b) Drug Notification Form

A completed, dated, and signed copy (also known as the Drug Identification Number [DIN] notification form) for all strengths and dosage forms.

c) Certified Product Information Document

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

d) Product Patent Expiration Date

e) Compendium of Pharmaceuticals and Specialties listing

A letter indicating the current or intended inclusion of the product monograph in the Compendium of Pharmaceuticals and Specialties (CPS).

f) Pharmaceutical Advertising Advisory Board (PAAB)-approved promotional materials — or a draft copy of material submitted to PAAB

If a Manufacturer does not intend to produce and use promotional material for the product, the Manufacturer may request that this requirement be waived. A letter signed by a senior company official stating the rationale and period of time (month and year) for which no promotional material will be used must be provided.

g) Economic and Epidemiologic Information

- Number of patients accessing the New Drug, pre-NOC, and post-NOC up to the time of the Submission, as compassionate supply from the Manufacturer, under the Special Access Program, or as part of a clinical trial
- Disease prevalence — the prevalence or incidence of the disease(s) or condition(s) for which the Drug is approved by Health Canada — should be provided for the Canadian population, with a breakdown by participating province, territory, and First Nations' population, where available (must be referenced)
- BIAs — if not already filed with Request for Priority Review based on cost savings — for each of the following Drug Plans, in accordance with their requirements: Newfoundland and Labrador, Prince Edward Island, Nova Scotia, New Brunswick, Ontario, Manitoba, Saskatchewan, Alberta, British Columbia, and Non-Insured Health Benefits Program (waivers may be granted upon submission of appropriate justification). 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 supporting documentation is required:

- all supporting information used in BIAs such as market research information or utilization reports
- copies of documents cited in the BIAs.

4.4.3 Additional Information

The following information may be requested by CADTH:

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 harm 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 the Health Canada Reviewers' Report for each Submission. To avoid delays in providing the Report to CADTH, Manufacturers are encouraged to request the Report from Health Canada as soon as they are assured that a NOC or NOC/c will be issued and to forward it immediately to CADTH. CADTH has not included the Health Canada Reviewers' Report as a Category 1 requirement in recognition that this report is not immediately available from Health Canada at the time that the NOC or NOC/c is issued but that Manufacturers often file Submissions with CADTH soon after receipt of a NOC or NOC/c.

c) Periodic Safety Update Reports

CADTH may request this information from the Manufacturer.

c) ***Clinical Study Report***

CADTH may request the Clinical Study Report or parts of it in searchable electronic format (Word or searchable PDF on CD).

5 RESUBMISSIONS

(Note: See section 5.3 for Resubmission based on Reduced List Price during Embargo Period.)

5.1 Resubmissions

Manufacturers, the FWG, and participating Drug Plans may file Resubmissions when they have New Information that was not provided in the original Submission or previous Resubmission(s).

New Information is new clinical information (not previously submitted or published) or new cost information that significantly impacts the cost-effectiveness of the Drug.

If the New Information is in support of improved efficacy, it must be from a randomized controlled trial. If the New Information is in support of improved safety, case-control or cohort studies will be accepted if randomized controlled trials are not available.

(Note: Information requested by CADTH to clarify a Submission is not considered New Information and does not affect the place of a Submission in the review queue.)

5.1.1 Eligible Resubmissions

Resubmissions from Manufacturers, the FWG, or Drug Plans are limited to New Drugs, New Combination Products, Drugs with New Indications, and Pre-NOC Submissions that are undergoing review through the CDR process or for which a Notice of Final Recommendation has been issued by CADTH. CADTH may accept Resubmissions under the following circumstances:

- New Information becomes available during the review process before the Notice of Final Recommendation has been issued; or
- A Reduced Price is offered by a Manufacturer during the Embargo Period when the CDEC Recommendation is "Do Not List" and the primary reason for the CDEC Recommendation is that the Drug is not cost-effective at the submitted price, and CDEC indicates this. (Note: A Manufacturer can offer a Reduced Price only when that Manufacturer has filed the Submission or Resubmission. In the situation where the FWG or a Drug Plan(s) has filed the Submission, Resubmission, or Request for Advice, a Manufacturer may file a Resubmission with a reduced price after the Notice of Final Recommendation is issued.) See section 5.3 for Resubmission based on Reduced List Price during Embargo Period; or
- New Information becomes available after Notice of Final CDEC Recommendation has been issued; or
- New Information becomes available that affects coverage criteria recommended by CDEC and accepted by the Drug Plans in their decisions to list a drug in their formularies.

5.1.2 Filing of Resubmissions

- With the exception of Resubmissions that are based on a Reduced Price during the Embargo Period, which may be submitted by email — Resubmissions must be delivered to CADTH by mail or courier (Appendix 4). Resubmissions cannot be filed electronically at this time.
- When initially filing a Resubmission, the Manufacturer should deliver only one complete copy of the Resubmission Requirements to CADTH in hard copy, plus one complete copy on CD, DVD, or memory stick, with all of the Resubmission Requirements (Note: Three CDs containing copies of the economic model in executable format are required with the initial Resubmission). The Manufacturer should wait until the Resubmission has been deemed complete by CADTH before submitting the required number of copies in the required format to CADTH as described in section 5.1.3, and to the participating Drug Plans as described in Appendix 1.
- Resubmissions based on Reduced Price during Embargo Period may be submitted by email, on CD, DVD, or memory stick.

5.1.3 Screening of Resubmission for Completeness and Required Number of Copies

- An initial screening of the Resubmission is conducted by CADTH within ten (10) days of receipt to ensure that it is complete.
- CADTH verifies whether the Resubmission is complete in accordance with this document.
- If the Resubmission is incomplete, CADTH sends a notice to the Manufacturer advising what information is needed to complete the Resubmission.
- When the Manufacturer's Resubmission is complete, CADTH sends an acknowledgement to the Manufacturer and advises the participating Drug Plans. Upon receipt of the acknowledgement, the Manufacturer must ensure that:

  - when the Resubmission is based on new clinical information, CADTH is provided with five (5) additional complete copies of the Resubmission in electronic format on CD, DVD, or PDF as specified in Appendix 7F, and five (5) hard copies of section 5.2.2 (e), "New Information" or, when the Resubmission is based on new cost information, CADTH is provided with three (3) complete copies of the Resubmission in electronic format on CD, DVD, or PDF, as specified in Appendix 7F and two (2) hard copies of section 5.2.2 (g), "Economic and Epidemiologic Information." (Note: Hard copies of the BIAs are required only if a Priority Review based on cost savings is submitted.)
  - each Drug Plan is provided with one or more copies of the Resubmission, or part of it, as directed by the Drug Plans in Appendix 1.
- In the case of a Resubmission based on a Reduced Price during the Embargo Period, when the Manufacturer's Resubmission is complete, CADTH sends an acknowledgement to the Manufacturer and advises the FWG and participating Drug Plans. No additional copies of the Resubmission are required from the Manufacturer by CADTH or by the Drug Plans.

5.1.4 Deadlines and Order of Review

Contained in section 4.1.5 of this document. The information for Submissions applies to Resubmissions as well.

5.1.5 Post-NOC Priority Review

Contained in section 4.1.7 of this document. The information for Submissions applies to Resubmissions as well.

5.1.6 Inquiries

Contained in section 4.1.9 of this document. The information for Submissions applies to Resubmissions as well.

5.1.7 Communications and Conflict of Interest

Contained in section 4.1.10 of this document. The information for Submissions applies to Resubmissions as well.

5.1.8 Confidentiality

Contained in section 4.1.11 of this document. The information for Submissions applies to Resubmissions as well.

5.2 Resubmission Requirements

The following table identifies the type of information that the Manufacturer must provide in filing a Resubmission, depending on when the Resubmission is being filed relative to the status of the Drug in the CDR process and the reason the Manufacturer is resubmitting.

Table 2: Guidance for Filing a Resubmission

When During the Review Process is the Resubmission Being Filed	Reason For Filing a Resubmission	What the Manufacturer Must Submit to CADTH
• Resubmission is filed before Notice of Final Recommendation is issued • Resubmission is filed after Notice of Final Recommendation is issued • Resubmission is based on New Information that affects coverage criteria and is filed after Notice of Final Recommendation is issued	New clinical information supporting improved efficacy	New randomized controlled clinical trial(s) and new pharmacoeconomic evaluation and BIAs
	New clinical information supporting improved safety	New case-control or cohort study (studies) and new pharmacoeconomic evaluation and BIAs
	New cost information	New pharmacoeconomic evaluation and BIAs
• Resubmission is filed after withdrawn market authorization has been re-instated		If Submission is withdrawn — all Submission requirements; If Resubmission is withdrawn — all Resubmission requirements. For both, Health Canada information addressing reason for withdrawal and reinstatement of market authorization.
• Resubmission is filed after voluntary withdrawal		Depending if Submission, Resubmission, or Request for Advice is withdrawn — all Submission, Resubmission, or Request for Advice requirements; updated documents (e.g., revised Product Monograph), any New Information (if applicable) and a list of changes since withdrawal.
• Resubmission is filed during Embargo Period if CDEC signals that lack of cost-effectiveness is main reason for "Do Not List" Recommendation	Reduced Price: CDEC notes in the recommendation document that a reduced price would increase cost-effectiveness	See section 5.3.

5.2.1 For Resubmissions Filed (as described in first three bullets in Table 2)

New Information, data, and reference material that were not included in the original Submission are required in addition to the information described in the following section "For All Resubmissions."

5.2.2 For All Resubmissions (except Resubmissions based on Reduced Price during Embargo Period)

Note: See section 5.3 for Resubmission based on Reduced List Price during Embargo Period.

The following information must be supplied when making any Resubmission and organized in the Resubmission binder with clearly labelled tabs identifying the sections (See Appendices 6 and 7D).

a) Signed Cover Letter

A signed cover letter (an electronic signature is acceptable) from Applicant, confirming that the information is new and stating the anticipated change or outcome. The letter should also provide:

- justification for the Resubmission — the rationale for the Resubmission

- whether the electronic versions (CD, DVD, or memory stick) of the Submission are included with the hard copy or being sent separately
- whether changes to the current Product Monograph are anticipated
- whether a Priority Review is being requested for the product and justification if requested
- justification for not providing a BIA for any of the ten (10) participating Drug Plans listed in Economic and Epidemiologic Information, in section 5.2.2 (g) of this document (if relevant)
- statement confirming that the submitted price is the current marketed price or the Confidential Price that may become effective following release of the CDEC Final Recommendation, section 5.2.2 (h)
- the names of the primary and backup contact(s) CADTH can contact regarding the Resubmission. (Note: The Manufacturer may designate the consultant(s) preparing the Submission as primary and/or backup contacts.) Any changes in contacts should be communicated to CADTH as soon as possible.

b) Table of Contents

A list of the contents and the page numbers on which they are found.

c) Executive Summary

A high-level summary of the Resubmission, including a brief description of the Drug and its place in therapy, a summary of the clinical and pharmacoeconomic evidence (including the unit cost), requested listing criteria, and the rationale (five pages maximum). When a Manufacturer has specified a restricted listing Recommendation (e.g., for a specific population), supporting references should be clearly identified in the Executive Summary.

d) Product Monograph

A copy of the most recent Product Monograph, showing the date it was approved by Health Canada and the company and product names that correspond to the NOC and an indication of whether and when changes to the current product monograph are anticipated.

e) New Information

- A list of all New Information not included in the original Submission, or previous Resubmissions, which is being included in the Resubmission
- Copies of all New Information and supporting documentation.
- Diagrams following the CONSORT reporting standards or similar diagrams that document the flow of patients through the trials, identified as pivotal trials in Health Canada documentation, in hard copy and electronic copy (PDF on CD). (Appendix 8 contains an example of the format and type of required information.) All information in the sections of the sample diagram is to be provided, including reasons for discontinuation and loss to follow-up at each stage of the study. If applicable, the following are to be incorporated into the CONSORT or similar diagram:
  - Additional phases of the study (e.g., screening, washout, baseline, treatment, follow-up) and reasons for discontinuing between phases;
  - Assessments at different time points and reasons for discontinuing between time points; and
  - Analysis populations for each outcome if they differ (primary outcome, key secondary outcomes, harms) and reasons why patients were excluded from each outcome analysis.
- An updated tabulated list of Canadian and international published and unpublished clinical trials that were not identified in the original Manufacturer's Submission to CADTH. The table should be provided in hard copy and as an electronic copy in Microsoft Word format on CD. (See Appendix 9 table template.) The template can also be downloaded from the CADTH website at www.cadth.ca. The list should include a list of all completed published studies, including

editorial articles and errata relating to them, unpublished studies, and a list of all ongoing studies for all indications.
- 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 trials have been disclosed (Appendix 10 letter template). The template may be downloaded from the CADTH website at www.cadth.ca.

f) Information if Drug has a Notice of Compliance with Conditions (NOC/c)
- Status of the confirmatory studies listed in the Letter of Undertaking if the Resubmission is for a Drug with an NOC/c
- Most recent interim analysis results for confirmatory studies listed in the Letter of Undertaking.

g) Economic and Epidemiologic Information
The following are required:
- An appropriate pharmacoeconomic evaluation for the full population identified in the approved Health Canada indication is required for all Resubmissions. If there are subgroups that may benefit from the Drug or specific reimbursement criteria requested by the Manufacturer, additional analyses should be provided. Refer to Appendix 15 for guidance on the type of economic analysis and what to submit. Please also refer to the CADTH document *Guidelines for the Economic Evaluation of Health Technologies: Canada.*
- Three (3) CDs containing copies of the economic model in executable format provided only in the Manufacturer's initial Resubmission sent for assessment of completeness. No additional copies are required by CADTH once the Resubmission is deemed complete. (Note: Copies of the economic model are not required in the Resubmissions sent to the participating Drug Plans.)
- The economic model must meet the following characteristics:
  - The submitted model is the basis for the economic evaluation.
  - The economic model must be in an unlocked (or executable) format; i.e., full access to the programming code is required and running of the model should be unhindered.
  - The economic model must be in one of the following formats: Excel, TreeAge / DATA, or Arena.
  - Documentation detailing the methods used in the modelling exercise and basic user information must be included.

  Note: Manufacturers are asked to contact CADTH in advance when they are using specialized programs to ensure that they meet CADTH's requirements and to receive direction on how the model and software should be provided in the Submission. Manufacturers are expected to provide CADTH with the necessary requirements to run the model (i.e., licences, laptop with model, and software), which will be returned to the Manufacturer at the end of the review process at the Manufacturer's expense.

  The CDR Reviewer must be able to vary individual parameters, view the calculations, and run the model to generate results. If statistical analyses of data sets are included in the model, the Manufacturer should provide a description of the data sources and analyses conducted and results from the analyses. The type of information that CDR requires for its examination of the model and the preferred format for receiving it are described in Table 3.

Table 3: CDR Pharmacoeconomic Information Requirements	
Information Elements	**Format**
Basis for the pharmacoeconomic study (model, spreadsheet)	A model* (or a spreadsheet) that is unlocked (or executable). The user should be able to specify inputs, view calculations, and run various analyses.
Media	CD-ROM or laptop
Software requirements	The Manufacturer must describe the software and system requirements to run the model. The submitted model must be in one of the following formats: Excel, TreeAge / DATA, or Arena. Where Manufacturers are using specialized programs, they are asked to contact CADTH in advance to ensure that the programs meet CADTH's requirements and to receive direction on how the model and software should be provided in the Submission. Manufacturers are expected to provide CADTH with the necessary requirements to run the model (i.e., licences, laptop with model, and software), which will be returned to the Manufacturer at the end of the review process at the Manufacturer's expense.
Basic user guide to the model	Hard copy and electronic format
Model documentation (manuscripts or a summary of the model report may be submitted)	Hard copy and electronic format
Description of the statistical analyses included in the model (data sources, methods, and results)	Hard copy and electronic format

*The model will be examined by internal and external CDR Reviewers. The model will not be released to any third parties.

- Number of patients accessing the New Drug, pre-NOC, and post-NOC, up to the time of the Submission, either as part of a compassionate supply from the Manufacturer, under the Special Access Program, or as part of a clinical trial
- Disease prevalence — the prevalence or incidence of the disease(s) or condition(s) for which the Drug is approved by Health Canada — should be provided for the Canadian population, with a breakdown by the participating province, territory, and First Nations' population, where available (must be referenced)
- BIAs (required in hard copy only if a Priority Review based on cost savings is requested) for each of the following Drug Plans, in accordance with their requirements: Newfoundland and Labrador, Prince Edward Island, Nova Scotia, New Brunswick, Ontario, Manitoba, Saskatchewan, Alberta, British Columbia, and Non-Insured Health Benefits Program (waivers may be granted upon submission of appropriate justification). 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 supporting documentation is required:
  - all supporting information used in BIAs such as market research information or utilization reports
  - copies of documents cited in the BIAs

If a Priority Review based on cost savings is requested for a Resubmission, the following are also required:

- Budget impact model (Excel spreadsheet), showing how the national cost savings is derived
- An explanation of the national budget impact analysis and the assumptions on which it is based.

h) Pricing Information

- Submitted prices reported as price per smallest unit to four decimal places and per smallest dispensable unit for all dosage forms, strengths, and package sizes. *(Note: The submitted price is the price that is effective for all participating Drug Plans. It can be the current market price in Canada or the Confidential Price effective for all participating 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.)*
  - If the submitted price is a Confidential Price that may become effective following release of the CDEC Final Recommendation, the Manufacturer must provide a signed commitment to honour this price for all participating Drug Plans (see Appendix 11 letter template).
  - Should issues arise regarding the submitted price, the participating drug plans may consider next steps, including the option of submitting a Request for Advice to CDEC about its Final Recommendation in considering the available current market price. This could potentially result in a changed Final Recommendation.
  - Only one current or Confidential Price per unit is to be submitted per Drug that under current CDR review (i.e., only one price for all indications undergoing CDR review concurrently).
  - The submitted price must be used in the pharmacoeconomic evaluation and in the BIAs included in the Resubmission.
- Method of distribution to pharmacies (wholesale, direct, or other arrangements).

i) Letter Authorizing Unrestricted Sharing of Information

This letter from the holder of the NOC or NOC/c, printed on company letterhead and signed by an appropriate senior official, should permit 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.

(See Appendix 12 letter template. The template may be downloaded from the CADTH website at www.cadth.ca.)

(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.)

j) Drug Notification Form

(Note: Also known as "Drug Identification Number [DIN] Notification Form.") For all strengths and dosage forms. A completed, dated, and signed copy of the most recent form(s) and copy(ies) of the original form(s). If no changes have been made to the original form, it should be submitted.

k) List of Decisions by Participating F/P/T Drug Plans

A summary of the benefit status of the Drug product in all participating F/P/T/ Drug Plans at the time of the Resubmission, including all criteria for coverage if applicable.

5.3 Requirements for Resubmission based on Reduced Price during Embargo Period

Signed Cover Letter

A signed cover letter (an electronic signature is acceptable) from a senior company official to CADTH and copied to all participating drug plans that:

- states what the Reduced Price is as price per smallest unit to four decimal places and per smallest dispensable unit for all dosage forms, strengths, and package sizes. (Note: Only one Reduced Price per unit is to be submitted); and
- indicates if the Reduced Price is a Confidential Price; and
- guarantees that the Reduced Price that may become effective following release of the CDEC Final Recommendation will be available to all of the participating drug plans; or
- guarantees that the Reduced Price, if submitted as a Confidential Price that may become effective following release of the CDEC Final Recommendation, will be available to all of the participating drug plans.

APPENDIX 1: Participating F/P/T Drug Plans

(Note: Manufacturers should send copies of Submissions and Resubmissions to participating F/P/T Drug Plans AFTER receiving confirmation from CADTH that the Submission or Resubmission is complete — i.e., that both Category 1 and 2 requirements are satisfied.)

Plan	Contact/Send Submission to:	What to Send
British Columbia*	Director, Formulary Management Pharmaceutical Services Division Ministry of Health 3-2 1515 Blanshard Street Victoria, BC V8W 3C8 T: 250-952-1183	One Complete Submission† in paper copy and one electronic copy on CD-ROM or DVD-ROM disc.
Alberta*	Mark Harasymuk A/Executive Director Pharmaceutical Funding and Guidance Alberta Health 10025 Jasper Avenue, 11th Floor P.O. Box 1360, STN Main Edmonton, AB T5J 2N3 T: 780-644-3835	One Complete Submission† in hard copy and in electronic format on CD or DVD.
Saskatchewan	Dr. Lorne Davis Pharmacologist College of Pharmacy and Nutrition Thorvaldson Building 110 Science Place University of Saskatchewan Saskatoon, SK S7N 5C9 T: 306-933-5599 Director, Pharmaceutical Services Drug Plan and Extended Benefits Branch Saskatchewan Health 3475 Albert Street, 2nd Floor East Regina, SK S4S 6X6 T: 306-787-3305	One Complete Submission† in hard copy for Dr. Lorne Davis. One Complete Submission† in electronic format on CD or DVD for Director, Pharmaceutical Services.
Manitoba	Kathy McDonald Secretary Drug Standards and Therapeutics Committee 1014-300 Carlton Street Winnipeg, MB R3B 3M9 T: 204-786-7317	One Complete Submission† in hard copy and one Complete Submission in electronic format on CD or DVD.
Ontario*	Director Ontario Public Drug Programs Ministry of Health and Long-Term Care 5700 Yonge Street, 3rd Floor Toronto, ON M2M 4K5 T: 416-327-8109	Three Complete Submissions in hard-copy format† plus pharmacoeconomic and BIA unlocked models on CD or DVD. Optional: one Complete Submission on CD or DVD.

Plan	Contact/Send Submission to:	What to Send
New Brunswick	Executive Director Pharmaceutical Services Department of Health P.O. Box 5100 520 King Street, 6th Floor Fredericton, NB E3B 5G8 T: 506-453-3884	One Complete Submission† in electronic format on CD or DVD.
Nova Scotia	Manager Insured Pharmaceutical Programs Nova Scotia Department of Health Joseph Howe Building 1690 Hollis Street Halifax, NS B3J 2R8 T: 902-424-1596	Executive Summary (two copies), NOC, Product Monograph, Pivotal Clinical Trials, BIA, and Prices.
Prince Edward Island	Pharmacy Consultant Health System Planning and Development Department of Health and Wellness P.O. Box 2000, 20 Fitzroy Street Charlottetown, PE C1A 7N8 T: 902-368-4947	One Complete Submission† in electronic format on CD or DVD.
Newfoundland and Labrador	Director Pharmaceutical Services Division Department of Health and Community Services 57 Margaret's Place St. John's, NL A1C 3Z3 T: 709-729-6507	One Complete Submission† in electronic format on CD or DVD.
Northwest Territories	Manager Health Services Administration Territorial Services Department of Health and Social Services Bag Service #9 Inuvik, NT X0E 0T0 T: 867-777-7412	Product Monograph, NOC, and Prices.
Yukon Territory	Dorothea Talsma Manager, Extended Benefits and Pharmaceutical Services Insured Health and Hearing Services (H-2) Government of Yukon 4th Floor, 204 Lambert Street (Box 2703) Whitehorse, YT Y1A 2C6 T: 867-667-5628	One Complete Submission† on CD or DVD.
Nunavut Territory		None
Non-Insured Health Benefits (NIHB)	Manager, Pharmacy Unit, Benefit Management Non-Insured Health Benefits First Nations and Inuit Health Branch Health Canada 200 Eglantine Driveway Postal Locator 1902A Ottawa, ON K1A 0K9 T: 613-957-7674	One Complete Submission† on CD or DVD.

Plan	Contact/Send Submission to:	What to Send
Department of National Defence (DND)‡	LCdr Sylvain Grenier Pharmacy Clinical Practice Leader Pharmacy Policy and Standards Department of National Defence 1745 Alta Vista Drive, Room 207 Ottawa, ON K1A 0K6 T: 613-945-6904	One Complete Submission‡ in electronic format on CD or DVD.
Veterans Affairs Canada (VAC)‡ Royal Canadian Mounted Police (RCMP)‡ Correctional Service Canada (CSC)‡	Rockie Palmer National Pharmacy Officer Veterans Affairs Canada 14 floor, 66 Slater St. , Ottawa, ON. K1A OP4 T: 613-944-5917	Three Complete Submission† in electronic format on CD or DVD. (*Note: Submissions for VAC, RCMP, and CSC* use.)

BIA = budget impact analysis

* Refer to the Drug Plan website for Drug Plan requirements.
†Complete Submission means that all of the Category 1 and Category 2 requirements are supplied; Manufacturers must prepare and provide BIAs for each of the participating provincial plans and NIHBP when they have the potential to list the particular product**.** The following Drug Plans have waived the requirement for a BIA: Northwest Territories, Yukon Territories, DND, VAC, RCMP, and CSC*.*
‡Although these Drug Plans have waived the requirement for a BIA to be prepared for them, each has requested copies of the BIAs prepared for other Drug Plans. Manufacturers should supply copies of all prepared BIAs to these federal Drug Plans.

(Note: When BIAs are not supplied for plans that have not waived the requirement, justification must be provided. In these cases, CADTH reviews the information and determines whether the Submission is complete. The Manufacturer is advised accordingly.)

When sending the Complete Submissions to the participating provincial Drug Plans and NIHB, Manufacturers have the option of including the BIAs for each of the different plans in the document (for example, Alberta would receive not only the BIA for Alberta, but also for the other plans) OR the Manufacturers may include only the plan-specific BIA in the Submission (e.g., Alberta would receive only the Alberta BIA).

APPENDIX 2: CDR Definitions

The following definitions shall apply to this document, unless otherwise stated.

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 Manufacturer by CADTH that is required to complete the review of the Submission or Resubmission, or to explain or clarify information related to the Submission or Resubmission. Providing this information does not affect the review queue; however, if there is a delay in providing it or if the quantity and complexity of the requested information is significant, there may be a consequent delay in completion of the review.

Applicant — the person, corporation, or entity filing a Submission or Resubmission.

Appropriate Comparator(s) — currently accepted therapy.

Budget Impact Analysis — an analysis of the impact of a new Drug product on Drug Plan expenditures.

Business Day — any day (other than a Saturday, Sunday, statutory holiday, or company holiday) on which the CADTH office in Ottawa, Ontario is open for business during regular business hours.

CADTH — Canadian Agency for Drugs and Technologies in Health, a corporate body, duly incorporated under the laws of Canada. It provides Canada's federal, provincial, and territorial health care decision makers with credible, impartial advice and evidence-based information about the effectiveness and efficiency of drugs and other health technologies.

CDEC — Canadian Drug Expert Committee, a CADTH advisory body composed of individuals with expertise in drug therapy and drug evaluation, and public members. It replaced CEDAC in September 2011. For drugs reviewed through the CDR process, CDEC makes formulary listing recommendations for use by the participating federal, provincial, and territorial publicly funded drug plans. CDEC also provides other drug-related recommendations or advice, based on CADTH reviews, to inform decisions and strategies including optimal use of drugs in Canada.

CDEC Brief — a brief prepared by CADTH staff for the members of CDEC, consisting of, but not limited to:

- the Manufacturer's Executive Summary of the Submission or Resubmission
- a list of unpublished studies known to the Manufacturer
- the Reviewers' Reports relating to the Submission or Resubmission
- the Manufacturer's written comments about the Reviewers' Reports
- the Reviewers' Replies, if any
- the Patient Group Input
- the related CADTH therapeutic review, if any.

CDEC Member — a member of the Canadian Drug Expert Committee (CDEC).

CDEC Recommendation — consists of the CDEC Recommendation regarding a Submission, Resubmission, or Request for Advice regarding a previous CEDAC or CDEC Recommendation and the Reasons for Recommendation.

CDEC Terms of Reference — the Terms of Reference established for CDEC by CADTH.

CEDAC — Canadian Expert Drug Advisory Committee. CEDAC was replaced by 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.

CDR — Common Drug Review. Under the CDR process, CADTH conducts objective, rigorous reviews of the clinical and cost effectiveness of drugs, and provides formulary listing recommendations to the publicly funded drug plans in Canada (except Quebec).

Clarifax — a Health Canada request for clarification that is faxed to the Manufacturer. The purpose of a Clarifax is to expand on, add precision to, or re-analyze existing information or data in the submission. Clarifaxes do not contain requests for new data, such as new Clinical and/or Pre-Clinical information, including bioavailability data that were not previously submitted**.**

Clarification — a written response, approved by the CDEC Chair, to a Drug Plan's Request for Clarification of a CDEC Recommendation.

Clinical Review — the review of published and unpublished information about the comparative safety, efficacy, effectiveness (when available), and use of a Drug in the management of a disease or condition.

Clinical Reviewer — a Reviewer who conducts a Clinical Review.

Code of Conduct — the code of conduct for CADTH committees, approved by CADTH's Board of Directors.

Combination Product (Funded Components) — a new combination product that contains two or more drugs that are already funded by the Drug Plans. One or more of the components may be non-prescription drugs, but at least one component must be a prescription drug. A Submission for this type of Combination Product is eligible for a tailored review by CDR.

Confidential Information — has the meaning given to it in the *CDR Confidentiality Guidelines.*

Confidentiality Guidelines — the guidelines respecting confidentiality adopted by the CADTH Board regarding CDR.

Confidential Price — a price per unit that is submitted in confidence as part of the CDR Submission Requirements and to which the provisions of the CDR Confidentiality Guidelines apply. Following the release of a CDEC recommendation to list or list with criteria, the submitted Confidential Price must be made available to all participating Drug Plans, whether or not the CDEC criteria for coverage are the same as the criteria requested by the Manufacturer. A listed market price is not considered confidential.

Conflict of Interest Guidelines — the conflict of interest guidelines adopted by CADTH for CDEC, Reviewers, and External Experts.

Directive — written information from CADTH amending, interpreting, updating, or clarifying any process, procedure, guideline, terms of reference, code of conduct, or document relating to the CDR.

Drug — an active substance considered to be a Drug under the Canadian Food and Drugs Act and Food and Drug Regulations, which is sold for human use.

Drug Plans — the participating publicly funded federal, provincial, and territorial Drug Plans.

Embargo Period — refers to a period of time (ten [10] Business Days) following the issuance of the Recommendation and Reasons for Recommendation or such extended period of time as may be granted by CADTH (under section 8.5.1 or section 8.6.1) during which the Recommendation and Reasons for Recommendation are neither acted on by Drug Plans nor are they publicly available. The Manufacturer also maintains the confidentiality of this document. During this period, the Manufacturer may submit a Request for Reconsideration or a Resubmission based on a Reduced Price, or the FWG or Drug Plans may submit a Request for Clarification.

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.

Final Recommendation — the applicable Recommendation, or Recommendation on Reconsideration, which contains the Reasons for Recommendation, attached to the Notice of Final Recommendation.

Formulary — a list of Drugs covered as benefits, as determined by each Drug Plan.

F/P/T — federal, provincial, and territorial.

FWG — Formulary Working Group, a working group of the Drug Policy Advisory Committee. FWG comprises representatives from the federal, provincial, and territorial publicly funded drug plans and other related health organizations. FWG provides advice to CADTH on pharmaceutical issues. Committee members also facilitate effective jurisdictional sharing of pharmaceutical information.

FWG Member — a member of the Formulary Working Group.

Information Specialist — a CADTH staff member who specializes in information retrieval and management in a health sciences research environment.

Manufacturer — a Drug Manufacturer.

New Active Substance — a therapeutic substance that has never before been approved for marketing 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

- a biological substance previously approved for sale in Canada as a Drug, but differing in molecular structure, nature of the source material, or manufacturing process.

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 CDR 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 NOC or NOC/c 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
- a biological substance previously approved for sale in Canada as a Drug, but differing in molecular structure, nature of the source material, or manufacturing process.

New Indication — a condition or disease that has not previously been approved for the use of the Drug.

New Information — new clinical information (not previously submitted or published) or new cost information that significantly impacts on the cost-effectiveness of the Drug and which does not form part of the original Submission or Resubmission. If the New Information is in support of improved efficacy, it must be in the form of a randomized controlled trial. If the New Information is in support of improved safety, case-control or cohort studies will be accepted if randomized controlled trials are unavailable.

Notice of Compliance (NOC) — authorization issued by Health Canada 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.

Notice of Deficiency — a document issued by Health Canada to a Manufacturer if deficiencies and/or significant omissions that preclude continuing the review are identified during the review of a submission.

Notice of Deficiency-Withdrawal (Letter) — if the response to a Notice of Deficiency is found to contain unsolicited information, is incomplete or deficient, the response to the Notice of Deficiency will be rejected and the submission will be considered withdrawn without prejudice to a refiling. A Notice of Deficiency-Withdrawal Letter will be issued by Health Canada.

Notice of Final Recommendation — the notice issued according to section 9 of the *Procedure for Common Drug Review.*

Notice of Non-Compliance — a document issued by Health Canada to a Manufacturer, if after the comprehensive review of a submission is complete, the submission is deficient or incomplete in complying with the requirements outlined in the *Food and Drugs Act and Regulations*.

Notice of Non-Compliance -Withdrawal Letter — if the response to a Notice of Non-Compliance is found to contain unsolicited information, is incomplete or deficient, the response to the Notice of Non-Compliance will be rejected and the Submission will be considered withdrawn without prejudice to a refiling. A Notice of Non-Compliance-Withdrawal Letter will be issued by Health Canada.

Old Drug — any Drug that is not a New Drug.

Overview of CDR Clinical and Pharmacoeconomic Review Reports (Overview) — a condensed version of the Final CDR Clinical Review Report and the CDR Pharmacoeconomic Review Report.

Participants — unless otherwise stated, CADTH staff, Reviewers, CDEC Members, and any experts retained to assist in the CDR process.

Patient Group — a patient group that is eligible to provide Patient Input to the CDR and CDEC processes as described in section 2 of the *Procedure for Common Drug Review*. Patient Groups may incorporate input from individual patients into their submissions to the CDR.

Patient Group 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 CDR Submission is indicated and the impact of drug therapy (existing and new, if available) on the lives of those with that illness or condition.

Pharmacoeconomic Review — the critical appraisal of the published and unpublished information about costs and consequences of Drugs and their impact on individuals, health care systems, and society (i.e., value for money of Drugs).

Pharmacoeconomic Reviewer — a Reviewer who conducts a Pharmacoeconomic Review.

Plain Language CDEC Final Recommendation — a version of the technical CDEC Final Recommendation that is written in non-technical language.

PMPRB — Patented Medicine Prices Review Board. PMPRB is an independent quasi-judicial body established by Parliament in 1987 under the *Patent Act*. The PMPRB has a dual role: (1) Regulatory **—** To ensure that prices charged by patentees for patented medicines sold in Canada are not excessive and (2) Reporting — To report on the pharmaceutical trends of all medicines and on the research and development spending by pharmaceutical patentees.

Pre-NOC Submission — a Submission for a New Drug for which Health Canada is highly likely to issue a NOC or NOC/c within ninety (90) Business 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 a NOC or a NOC/c will be issued on a particular date or at all, Manufacturers may consider filing a submission with CDR up to ninety (90) calendar days in advance of anticipated NOC or NOC/c if no significant issues have been raised by Health Canada.

Priority Review — a preferred status in the review queue and on the CDEC agenda for Drugs meeting the Post-NOC Priority Review Criteria. All steps in the CDR procedure are completed and timelines are not truncated.

Reasons for Recommendation — the detailed, written reasons given by CDEC regarding Recommendations, or Recommendations on Reconsideration, made by CDEC. The Reasons for Recommendation are released to the Manufacturer and Drug Plans only, and are not publicly available during the Embargo Period.

Recommendation — an evidence-based recommendation made by CDEC after consideration of Review Criteria, in response to a Submission or Resubmission made by a Manufacturer, the FWG, or one or more Drug Plans, or in response to a Request for Advice regarding a CDEC Recommendation or Reasons for Recommendation made by the FWG, or one or more Drug Plans. The Recommendation is released to the Manufacturer and Drug Plans only, and is not publicly available during the Embargo Period.

Recommendation on Reconsideration — the conclusion reached by CDEC on reconsideration of the Submission or Resubmission, as described in section 8.5.4 of the *Procedure for Common Drug Review.*

Reconsideration Brief — the CDEC Brief, CDEC Recommendation, CDEC Reasons for Recommendation, and Request for Reconsideration.

Record of Advice — the detailed advice given by CDEC in reply to a Request for Advice.

Reduced Price — a price that is less than the price submitted in a Submission or Resubmission and is required for a Resubmission based on a Reduced Price during the Embargo Period. It is provided as price per smallest unit to four decimal places and per smallest dispensable unit for all dosage forms, strengths, and package sizes. It can be a Confidential Price.

Reply — a response by a Reviewer to a Manufacturer's Comments about a Clinical or Pharmacoeconomic Review conducted by that Reviewer.

Report — a report produced by a Reviewer.

Request for Advice — a written request made by the FWG or by one or more Drug Plans to CDEC for advice on specific therapeutic**,** clinical or pharmacoeconomic issues, or regarding a CDEC Recommendation or Reasons for Recommendation, which may result in a new Recommendation.

Request for Clarification — a written request from a Drug Plan for clarification of a CDEC Recommendation.

Request for Reconsideration — a written request from Manufacturers to have a CDEC Recommendation reconsidered.

Request for Withdrawal — a written request by an Applicant to withdraw a Submission or Resubmission from the review process.

Resubmission — the request by a Manufacturer, Drug Plan, or the FWG to have an original Submission, that is under review or has received a Notice of Final Recommendation, reviewed again

through the CDR process on the basis of New Information that was not previously provided in the original Submission or considered by CEDAC or CDEC. The Resubmission goes to the end of the review queue.

Review Criteria — the following criteria are considered by CDEC in making a listing recommendation:

- clinical studies, which assess safety and/or efficacy of the Drug in appropriate populations (when available, effectiveness data will be compared with current accepted therapy)
- therapeutic advantages and disadvantages relative to current accepted therapy
- cost-effectiveness relative to current accepted therapy
- patient perspectives obtained through Patient Group Input.

Review Team — a team of individuals (including CDR Staff Reviewers, Contracted Reviewers and External Experts [clinical experts, methodologists, or other experts] with appropriate qualifications and expertise) assembled by CADTH to undertake the review of a Submission or Resubmission, or to prepare a Report in response to a Request for Advice.

Review Template — a template developed by CADTH for use by Reviewers to prepare Review Reports that are consistent in the type of content and format.

Reviewer — an expert selected to conduct a Clinical or Pharmacoeconomic Review.

Stopped (a review) — refers to the cessation of the review of a Submission or Resubmission under the CDR process before all steps of the review process are completed. Work on a stopped Submission or Resubmission does not resume—a new Submission or Resubmission is required if the Applicant wishes to have the Drug reviewed. A review is stopped in the following circumstances:

- when Health Canada issues a Notice of Non-Compliance or Notice of Deficiency or withdraws market authorization of a Drug that is the subject of a Submission or Resubmission under review; or
- when an Applicant has voluntarily withdrawn a Submission or Resubmission and the FWG and participating drug plans are in agreement; or
- when an Applicant files a Resubmission while a Submission is under review but before the Notice of Final Recommendation has been issued—i.e., the review of the Submission is stopped.

Submission — a submission to the CDR consisting of:

- a written application made by a Manufacturer, together with supporting documentation, to have a Drug listed on the Drug Plans' Formularies; or
- a written request, together with supporting documentation, if any, made by the FWG or by one or more Drug Plans, to consider the listing status of Drugs already on Formularies, to conduct Drug class reviews, or to undertake any other Drug-related review(s), as required.

Submission Guidelines — the guidelines adopted by CADTH that outline how Submissions from Manufacturers must be prepared and submitted.

Submission Requirements — information that is required by CADTH to undertake the Clinical and Pharmacoeconomic Reviews of Drugs and other information that is required by the Drug Plans in making listing decisions. The Submission Requirements consolidate the requirements for the CDR and the Drug Plans. The Requirements apply to Submissions and Resubmissions.

Suspended (a review) — refers to the temporary cessation of the review of a Submission or Resubmission under the CDR process. This occurs if questions or issues arise outside of the regular review process. Once the issue is resolved the review proceeds from the point at which it was suspended. The Applicant is not required to file a Submission or Resubmission to re-initiate the review.

Systematic Review — involves a review of a clearly formulated question using systematic and explicit methods to identify, critically appraise, and summarize relevant studies (published and unpublished) according to predetermined criteria. Reported outcomes can be synthesized either quantitatively or as a narrative to summarize the results of included studies.

Technical Version of the CDEC Final Recommendation — a version of the CDEC Final Recommendation that uses extensive scientific and medical terminology to describe the Recommendation and Reasons for Recommendation.

Therapeutic Review — a review of publicly available evidence regarding a single drug (e.g., enalapril), or a category of drugs (e.g., angiotensin-converting-enzyme inhibitors [ACEIs]), or a class of Drugs (e.g., antihypertensive agents). The scope and depth of the review are determined by jurisdictional needs. An important characteristic of a therapeutic review is that it is conducted to coincide with a CDR submission review, and thus, informs the CDR submission review and listing recommendation and informs Drug Plan decisions.

APPENDIX 3: Clarification of Where Submissions for Specialty Drugs Should Be Filed (Cancer or HIV/AIDS Drugs)

All Submissions for oncology drugs, used in the active treatment of cancers, should be sent to the pan-Canadian Oncology Drug Review (pCODR). See the pCODR website for information, www.pcodr.ca

Many of the participating Drug Plans review and consider coverage for specialty products, such as HIV/AIDS drugs, and therefore a complete Submission to CADTH is required. However, some provinces have separate review and reimbursement agencies for specialty products. For example, the BC Centre of Excellence for HIV/AIDS reviews all HIV/AIDS drugs for British Columbia and, therefore, documentation for the BC Drug Plan is not required in the CDR Submission.

The following summary provides general guidelines for Manufacturers about where Submissions for HIV/AIDS Drugs (New Drugs and New Combination Products) should be sent.

(Note: These are general guidelines only; whenever there is doubt about whether a Submission should be made to CADTH, Manufacturers are asked to contact CADTH for direction.)

Table 1: Where to File Specialty Drugs Submissions

Province	Oral HIV/AIDS Drugs
British Columbia	Send to Centre of Excellence in HIV/AIDS
Alberta	Send to Alberta Health and Wellness
Saskatchewan	Send to CADTH
Manitoba	Send to CADTH
Ontario	Send to CADTH
New Brunswick	Send to CADTH
Nova Scotia	Send to CADTH
Newfoundland and Labrador	Send to CADTH
Prince Edward Island	Send to CADTH
Northwest Territories	Send to CADTH
Yukon Territories	Send to CADTH
Federal — Participating Drug Plans	Send to CADTH

AIDS = acquired immunodeficiency syndrome; CADTH = Canadian Agency for Drugs and Technologies in Health; HIV = human immunodeficiency virus.

APPENDIX 4: Delivery of Mail and Documents

a) Process and Means

Any notice, request, document, or other communication (collectively "Communications") to be given in connection with the CDR procedure shall be, except as otherwise provided in these procedures, given in writing and shall be given by personal delivery, by registered mail, or by facsimile or other electronic means of communication addressed to the recipient, as follows:

To:

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

To an Applicant:

The address set out in the Submission, Resubmission, or Request for Advice or to such other address or electronic communication number as may be designated by notice given in accordance herewith.

To Another Person or Corporation:

The address or electronic communication number as may be designated by notice given in accordance herewith.

b) Delivery Times

Any Communications will be considered to have been delivered:

- on the day of actual delivery, if by personal delivery
- on the fifth (5^{th}) day following deposit in the mail, if by registered or regular mail
- on the day of transmittal if sent during the normal business hours of the recipient or on the Business Day during which such normal business hours next occur, if by electronic means.

If the party sending Communications knows, or ought reasonably to know, of any disruption or difficulty with the postal system that might affect the delivery of mail, any such Communications shall not be mailed but shall be given by personal delivery or by electronic communication.

c) Determining Time Frames

The date on which the Submission or Resubmission is received is considered day zero (0) for the purpose of calculating time frames.

The date on which CADTH receives a Request for Advice is considered day zero (0) for the purpose of calculating time frames.

APPENDIX 5: CDR Confidentiality Guidelines

The Canadian Agency for Drugs and Technologies in Health (CADTH) has developed the following Confidentiality Guidelines to ensure the Confidential Information obtained for the purpose of the Common Drug Review (CDR) process is protected. These guidelines ensure appropriate steps and procedures are in place and that Confidential Information is handled in a consistent manner. CADTH complies with these Confidentiality Guidelines when handling information, as part of the CDR process. A Manufacturer is deemed to have consented to the Confidentiality Guidelines by filing a Submission or by supplying other information to CADTH for the CDR process. These Confidentiality Guidelines constitute an agreement between CADTH and the Manufacturer. A Manufacturer and all authorized recipients, named in this document, will maintain the confidentiality of documents that CADTH shares with them that are labelled as "Confidential."

Definition

"Confidential Information" (including Confidential Price) is information supplied by a Manufacturer. It includes any non-public scientific, technical, or commercial information about a Manufacturer's business or a Manufacturer's product received as a result of the exchange of information as part of the CDR process, but which does not include information that:

a) was already in the possession of CADTH, External Reviewer(s) assigned to review the Submission or Resubmission, CDEC Members, External Experts (when contracted to provide specific information in relation to the Submission or Resubmission), Formulary Working Group (FWG) Members, federal/provincial/territorial (F/P/T) governments, F/P/T health authorities, Drug Plans, Health Canada, or the Patented Medicine Prices Review Board (PMPRB), without restriction as to its use or disclosure;

b) is or becomes available to the general public other than as a result of a breach of the procedures contained herein (information available to the general public includes but is not limited to published articles, Drug prices, and product monographs); or

c) a third party (who is not under any obligation as to confidentiality or non-disclosure) rightfully discloses to CADTH, External Reviewer(s) assigned to review the Submission or Resubmission, CDEC Members, External Experts (when contracted to provide specific information in relation to the Submission or Resubmission), FWG Members, federal/provincial/territorial (F/P/T) governments, F/P/T health authorities, Drug Plans, Health Canada, or PMPRB, without restriction as to its use or disclosure.

Confidential Information shall be marked as "Proprietary" or "Confidential," with an appropriate legend, marking stamp, or other obvious written identification by the Manufacturer. Only information that has not previously been made public and is confidential should be labelled or identified as such.

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

Access to Information and Freedom of Information Legislation

CADTH is a private, not-for-profit organization and is therefore not subject to either federal access to information or provincial/territorial freedom of information statutes. However, Manufacturers are asked to consent to their information being exchanged with F/P/T governments, F/P/T health authorities, Drug Plans, Health Canada, and the PMPRB by signing a letter in the form available in the Manufacturers' Submission Guidelines. These bodies have their own confidentiality procedures and are subject to provincial or federal freedom of information and access to information legislation. CADTH has no jurisdiction or control over those procedures and statutory requirements. Manufacturers should be aware of those procedures and requirements when including Confidential Information in a Submission or Resubmission.

Handling Confidential Information

1. Responsibilities of CADTH

a) CADTH will use reasonable care to prevent the unauthorized use, disclosure, publication, or dissemination of Confidential Information that is included in and related to Manufacturers' Submissions and Resubmissions, and labelled "Proprietary" or "Confidential;"

b) CADTH will not disclose Confidential Information in and related to the Manufacturers' Submissions or Resubmissions to any third party except as permitted by these Confidentiality Guidelines, or as required by law or by order of a legally qualified court or tribunal;

c) CADTH will use the Manufacturer's Submission or Resubmission and Confidential Information solely for the purpose of carrying out its responsibilities with respect to the Common Drug Review;

d) CADTH has in place secure filing and storage, websites, and processes for tracking Manufacturers' Submissions or Resubmissions and Confidential Information;

e) CADTH has in place internal processes for dealing with Manufacturers' Submissions or Resubmissions and Confidential Information in hard copy and electronic format, as described in the following sections.

2. Release of Manufacturer's Information

a) A Manufacturer's Submission or Resubmission, including the Manufacturer's Confidential Information, may be released to the following (the "Authorized Recipients"):
- CADTH Staff
- Review Team
- CDEC Members
- FWG Members
- F/P/T governments and Drug Plans
- F/P/T health authorities
- Health Canada
- PMPRB.

b) CADTH Staff are required, as a condition of employment, to comply with CADTH's confidentiality requirements, Code of Conduct, and Conflict of Interest guidelines.

c) All Reviewers, CDEC members, and Expert Advisors must abide by the confidentiality clauses contained in their Code of Conduct and/or Conflict of Interest Guidelines and/or contracts.

d) FWG members are required to sign a non-disclosure agreement requiring them to comply with these Guidelines. (Note: Drug Plans, F/P/T governments, F/P/T health authorities, Health Canada, and the PMPRB are not required to sign non-disclosure agreements, as they have their own processes and statutory requirements to address confidentiality issues, as previously described.)

e) The Manufacturer's Submission or Resubmission, or parts of it, including Confidential Information, may be discussed amongst any or all of the bodies named in the letter signed by the Manufacturer authorizing unrestricted communication about the Drug.

f) In the case of a Pre-NOC Submission, information regarding the Manufacturer's product, including Clarifaxes and other relevant information, may be shared between Health Canada and CADTH, as authorized in a signed letter from the Manufacturer.

3. Documents that May Be Shared with Authorized Recipients

a) The following documents and the information contained in them, including Confidential Information, may be shared with the Authorized Recipients and may be posted on a confidential website accessible only by persons authorized according to these Confidentiality Guidelines:
- Manufacturer's Submission or Resubmission
- Reviewers' Reports
- Manufacturer's Comments About Reviewers' Reports
- Reviewers' Replies to Manufacturer's Comments
- CDEC Recommendation
- CDEC Brief
- CDEC Reconsideration Brief.

b) The following documents are shared with a Manufacturer with respect to Submissions or Resubmissions, or in respect to a Drug Plan Submission or Resubmission that affects the Manufacturer's Drug or a Request for Advice about a Recommendation that may result in a new Recommendation. The Manufacturer maintains the confidentiality of these documents.
- Reviewers' Reports
- CDEC Recommendation
- CDEC Recommendation on Reconsideration
- Plain Language CDEC Final Recommendation (until posted on CADTH website)
- Response to Request for Clarification
- Request for Advice

c) The following documents are posted on the CADTH website:
   - Tracking document indicating the status of a Drug, including a Pre-NOC Submission, in the review queue.
   - CDEC Final Recommendation with Confidential Information removed (both the Technical version and the Plain Language version)

d) Information regarding the Manufacturer's product, including Clarifaxes and other relevant information, may be shared between Health Canada and CADTH, as authorized in a signed letter from the Manufacturer (e.g., Pre-NOC Submission).

4. Referring to Manufacturer's Confidential Information in the CDR Publicly Available Documents (i.e., the Documents Posted on the CADTH Website)

In the preparation of the CDR Clinical Review Report and the CDR Pharmacoeconomic Review Report, CADTH may use unpublished studies or the Confidential Price supplied by the Manufacturer, in addition to the evidence that CADTH identifies and compiles regarding the Drug. These reports, which form the basis for the CDEC Reasons for Recommendation and other CDR publicly available documents, may contain Confidential Information (including Confidential Price), as identified by the Manufacturer. In such cases, the following provisions shall apply:

Technical and Plain Language Recommendation Documents

The Technical version and the Plain Language Recommendation documents may contain Confidential Information. Each document will be sent to the Manufacturer, who will be asked to identify any Confidential Information to be redacted in both the Technical and Plain Language versions of the Final Recommendation.

If the Manufacturer instructs that the Confidential Information be deleted from the CDEC Final Recommendation:

- CADTH will redact the Confidential Information by removing it and will indicate:
  - that Confidential Information was used by CDEC to make its listing Recommendation; and
  - that the Manufacturer requested that the Confidential Information be deleted, pursuant to the CDR Confidentiality Guidelines.
- CADTH will describe the quantity of information that was redacted and will provide a general description of the type of information (e.g., Confidential Price, unpublished study results, etc.) that was redacted.
- If the Confidential Information is mentioned in any public document, CADTH may make reference to the name of the study or such relevant information.

5. CDEC Minutes

Minutes of the CDEC meetings are released only to CDEC members, and to the President and Chief Executive Officer of CADTH.

6. Archiving of Documents Containing Confidential Information

a) One complete set of all paper and electronic documents, including documents containing Confidential Information associated with the review of a Drug, is kept on file in secure storage for as long as there may be a need to consult them. CADTH staff undertake regular reviews of

archived material. Any material that CADTH determines to be no longer required is disposed of, as subsequently described in section 7.

b) Extra copies of paper and electronic documents associated with the review of a Drug are disposed of, as subsequently described in section 7.

7. Disposal of Documents Containing Confidential Information

a) CADTH disposes of extra copies of the Submission or Resubmission, including documents containing Confidential Information supplied by a Manufacturer, by confidential shredding. (Note: One complete set of all documents [paper and electronic] associated with the review of a Drug is kept on file, as described above in section 6.)

b) CADTH advises the Manufacturer, in writing, that it has disposed of extra copies of documents.

c) Reviewers are requested to delete and confirm the deletion of all Confidential Information in their electronic files.

APPENDIX 6: Format of Submissions and Resubmissions

The Manufacturers' Submission Requirements for New Drugs, New Combination Products, Drugs with New Indications, Pre-NOC Submissions, and the Resubmission Requirements have been developed to assist Manufacturers in providing the information required by CADTH and participating Drug Plans.

Manufacturers are invited to use the Submission and Resubmission Checklists (for CADTH Use) in Appendix 7 of this document to ensure that each Submission or Resubmission is complete. An incomplete Submission or Resubmission leads to delays in the process and may be returned to the Manufacturer at the discretion of CADTH staff, at the Manufacturer's expense. An incomplete Submission or Resubmission does not enter the CDR process until all of the required Category 1 information is deemed complete by CADTH. A Submission is not placed on the CDEC agenda until all of the Category 2 information is received. In the case of a Pre-NOC Submission, the Submission is placed on the CDEC agenda, but the Notice of Final Recommendation is not issued until the Category 2 requirements are complete.

Various letter templates, review templates, and worksheets are contained within this document as appendices to assist with the completion of the Submission and Resubmission. This document and the templates are also available on the CADTH website, www.cadth.ca.

The following guidelines are provided to assist Manufacturers in the preparation and organization of Submissions and Resubmissions:

- Submissions and Resubmissions must be provided in hard copy at this time.
- All Category 1 requirements must be included in the Submission and Resubmission (if applicable) so that steps may be taken to initiate the review.
- If a Manufacturer requests a Priority Review based on cost savings, BIAs must be submitted at the time of filing a Submission and Resubmission.
- The Clinical Studies section of the Comprehensive Summary will be accepted by CADTH during the transition to the Common Technical Document for New Drug Submissions made to Health Canada. Synopses of individual studies must also be included.
- All Category 2 information must be provided as a single package in electronic format only at least twenty (20) Business Days prior to the targeted CDEC meeting at which the Submission or Resubmission (if applicable) will be considered. In the case of a Pre-NOC Submission, the Submission requirements must be met within twenty (20) Business Days of the Manufacturer's receipt of the NOC or NOC/c.
- Submissions must be organized in the order outlined in the CDR "Submission Requirements for New Drugs, New Combination Products, and Drugs with New Indications" (section 4.2 of this document); Pre-NOC Submissions must be organized in the order outlined in the Pre-NOC Submission Requirements (section 4.3 of this document); Submissions for New Combination Products (Funded Components) must be organized as described in section 4.4 of this document; and Resubmissions must be organized as described in Resubmission Requirements (section 5.2 of this document).
- All pages of the Category 1 requirements in the Submission and Resubmission (if applicable) should be numbered consecutively from beginning to end. All pages of the Category 2 requirements should be numbered separately (i.e., starting at page 1 again) from beginning to

end. It is also acceptable to number the pages consecutively within each section, but the section and page number must be clearly identified on each page.

- Binders should be sturdy and not overfilled. The maximum thickness of binders should not exceed seven (7) centimetres [three (3) inches].
- Each binder should be clearly labelled with the name of the Drug, Manufacturer, date, binder x (number) of y (total number of binders).
- Double-sided pages should be used.
- All files submitted electronically should be labelled with the brand name of the Submission or Resubmission and the type of file. (See Appendix 7F.)
- Each section of the Submission and Resubmission must be identified with large tabs that are clearly labelled with the section name.
- The Submission or Resubmission is to be provided in English. All submitted articles should be in English. Unpublished data may be submitted. To be appraised, the unpublished studies should include the following:
  - Objective and rationale of study
  - Study population (including eligibility criteria, baseline characteristics, and sample size)
  - Methods (including blinding, handling of withdrawals and drop-outs, allocation concealment, and outcome measurement)
  - Results (all beneficial and harmful patient effects including an itemization of fatal and non-fatal serious adverse events; number of withdrawals and drop-outs, with reasons; measure of dispersion such as standard deviation or standard error must be provided for continuous outcomes; numerators and denominators must be provided for dichotomous outcomes)
  - Data analysis
  - Conclusions.

Although it is preferred that unpublished data be submitted in manuscript format, manuscript format is not a requirement. When unpublished data are not submitted in manuscript format, the information listed above should be included in clearly labelled sections. Only information that is truly confidential should be labelled as such. (See Confidentiality Guidelines, Appendix 5.)

Submissions and Resubmissions should be sent to:

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

Telephone: 613-226-2553

APPENDIX 7: Submission and Resubmission Checklists

Drug Name: _____

Manufacturer: _____

Category and Designation:

New Drug	☐
New Combination	☐
Combination (funded components)	☐
Drug with New Indication	☐
Pre-NOC Submission	☐
Drug Plan Request	☐

Submission Type:

First review	☐	File number:	_____
Resubmission	☐	File number:	_____

Priority Review Submission:

Post-NOC Priority Review Submission	☐
Request for Priority Review	☐
Justification provided	☐

Administrative Information:

Complete set of Category 1 (or 1 & 2) Submission Requirements provided _____
(See list of Submission Requirements)

Number of binders that make up Submission set = total x

Category 1 = x binder
Category 2 = x binder

Number of CDs/DVDs/memory sticks = total x
Economic model (3 CDs required) = x
Submission requirements = x

APPENDIX 7A

Submission Requirements Checklist: Category 1

(Required in hard copy and in electronic format as CD, DVD, or memory stick. See Appendix 7F for electronic submission specifications.)

Signed Cover Letter	□
• Whether CDs/DVDs/memory sticks are included with hard submission	□
• Priority Review request and justification (if applying for Priority Review)	□
• Confirmation that submitted price is current market price or Confidential Price	□
• Justification for not providing a Budget Impact Analysis (BIA) for a specific jurisdiction (if relevant)	□
• The New Indication when submitting a Drug with New Indications	□
• Names of primary and backup contacts to be contacted regarding Submission.	□
Table of Contents	□
Executive Summary	□
• Supporting references for specified listing when requested by Manufacturer.	□
Health Canada NOC or NOC/c (dated and signed) for indication under review	□
• Letter of Undertaking (if NOC/c).	□
Product Monograph	
Product Monograph	□
• **Efficacy, Effectiveness, and Safety Evidence**	
Clinical Overview and Clinical Summary, including synopses of individual studies (Common Technical Document, Modules 2.5, 2.7.1, 2.7.3, 2.7.4, and 2.7.6, which includes list and individual study synopses) OR Clinical Studies section of Comprehensive Summary	□
• Critical studies that address key clinical issues (published and unpublished)	□
• Diagrams following CONSORT reporting standards or similar diagrams, documenting flow of patients through studies	□
• Copies of editorial articles and errata relating to published studies	□
• New data generated since the last date that data were reported in studies included in Submission	□
• Copies of references supporting validity of outcome measures OR statement confirming that a search did not identify any	□
• Tabulated list of published and unpublished studies — hard copy and Word format (Appendix 9)	□
• Search strategies	□
• Signed declaration that all unpublished studies have been disclosed.	□
Economic and Epidemiologic Information	
Pharmacoeconomic Evaluation for the full population in the approved Health Canada indication	□
• Three CDs with copies of economic model and documentation (with initial Submission only)	□

• Number of patients accessing drugs Pre-NOC and Post-NOC until submitted [not required for Drugs with New Indication(s)]	□
• Disease prevalence and incidence data with breakdown where available	□
• BIAs provided with the initial Submissions if Priority Review requested based on cost savings	□
▪ Newfoundland and Labrador	□
▪ Prince Edward Island	□
▪ Nova Scotia	□
▪ New Brunswick	□
▪ Ontario	□
▪ Manitoba	□
▪ Saskatchewan	□
▪ Alberta	□
▪ British Columbia	□
▪ Non-Insured Health Benefits Program.	□
Supporting Documentation for the BIAs includes:	□
▪ Documentation of all market research or utilization information used in BIAs	□
▪ Copies of documents cited in the BIAs.	□
▪ Budget Impact Model [for Priority Reviews based on cost savings]	□
▪ National Budget Impact analysis document [for Priority Reviews based on cost savings]	□
Pricing and Availability Information	
Submitted pricing reported as price per smallest unit to four decimal places	□
• Signed commitment if submitted price is Confidential Price (Appendix 11)	□
• Method of distribution.	□
Letter Authorizing Unrestricted Sharing of Information	□

Submission Requirements Checklist: Category 2

(To be provided as a single package twenty [20] Business Days prior to the targeted CDEC *meeting)*

CADTH requires only one (1) complete set of Category 2 Submission Requirements in electronic format only (i.e., CD, DVD, or memory stick).

Letter Confirming Ability to Supply	□
Drug Notification Form (Drug Identification Number Notification Form) for all strengths and dosage forms, **Dated and Signed**	□
Certified Product Information Document (CPID)	□
Product Patent Expiration Date	□
Compendium of Pharmaceuticals and Specialties Listing Intention Letter	□
Pharmaceutical Advertising Advisory Board (PAAB)-Approved Promotional Materials (or Draft Copy of Material Submitted to PAAB) or Letter Requesting Waiver	□
Economic and Epidemiologic Information	
• Number of patients accessing drugs Pre-NOC and Post-NOC until submitted	□
• Disease prevalence and incidence data with breakdown where available	□
• BIAs (If not provided with Category 1 requirements)	□
▪ Newfoundland and Labrador	□
▪ Prince Edward Island	□
▪ Nova Scotia	□
▪ New Brunswick	□
▪ Ontario	□
▪ Manitoba	□
▪ Saskatchewan	□
▪ Alberta	□
▪ British Columbia	□
▪ NIHB	□
Supporting Documentation for the BIAs includes:	□
▪ documentation of all market research or utilization information used in BIAs	□
▪ copies of documents cited in the BIAs.	□

APPENDIX 7B

Pre-NOC Submission Requirements Checklist: Category 1

(Note: It is the responsibility of the Manufacturer to advise Health Canada of the intent to file a Pre-NOC Submission with the CDR Directorate.)

(Required in hard copy and in electronic format as CD, DVD, or memory stick. See Appendix 7F for electronic submission specifications.)

Signed Cover Letter • Description of Submission being filed • Whether CDs/DVDs/memory sticks are included with hard submission • Confirmation of intention to provide Category 2 requirements within twenty (20) business days of NOC or NOC/c • Justification for not providing a Budget Impact Analysis (BIA) for a specific jurisdiction (if relevant) • Confirmation that submitted price is current market price or Confidential material • Names of primary and back-up contacts regarding Submission	□ □ □ □ □ □
Table of Contents	
Screening Acceptance Letter	□
Executive Summary • Supporting references for specified listing when requested by Manufacturer	□ □
Health Canada NOC or NOC/c (dated and signed)—**as soon as available** • Letter of Undertaking (if NOC/c)—**as soon as available**	□ □
Product Monograph (draft to CDR only) (final to CDR and drug plans as soon as available)	□
Efficacy, Effectiveness and Safety Evidence • Clinical Overview and Clinical Summary, including Synopses of Individual Studies (Common Technical Document, Modules 2.5, 2.7.1, 2.7.3, 2.7.4 and 2.7.6, which includes list and individual study synopses) • Copies of critical studies that address key clinical issues (published and unpublished) • Diagrams following CONSORT reporting standards or similar diagrams documenting flow of patients through studies • Copies of editorial articles and errata relating to published studies • New data generated since the last date that data were reported in studies included in Submission • Copies of references supporting validity of outcome measure OR statement confirming that a search did not identify any • Tabulated list of published and unpublished studies — hard copy and Word format (Appendix 9) • Search strategies • Signed declaration that all unpublished studies have been disclose	□ □ □ □ □ □ □ □ □ □

Economic and Epidemiologic Information	
• Pharmacoeconomic Evaluation for the full population in the approved Health Canada indication	□
• Three CDs with copies of unlocked economic model and documentation	□
• Number of Patients Accessing Drugs Pre-NOC and Post-NOC Until Submitted [not required for Drugs with New Indication(s)]	□
• Disease Prevalence and Incidence Data With Required Breakdown Where Available	□
Pricing and Availability Information	□
• Submitted pricing reported as price per smallest unit to four decimal places	□
• Signed commitment if submitted price is Confidential Price	□
• Method of distribution.	□
Letter Authorizing Unrestricted Sharing of Information	□
Letter of Authorization allowing Health Canada to share information with CDR	□
Completed form indicating what information Health Canada can share with CDR	□
Table of Clarifaxes that have been provided	□
Copies of Clarifaxes	□

Pre-NOC Submission Requirements Checklist: Category 2

(Note: To be provided as a single package within twenty (20) Business Days of receiving NOC)

CADTH requires only one (1) complete set of Category 2 Submission Requirements in electronic format only (i.e., CD, DVD, or memory stick).

Signed Cover Letter	□
Letter Confirming Ability to Supply	□
Drug Notification Form (Drug Identification Number Notification Form) for all strengths and dosage forms, dated and signed	□
Certified Product Information Document (CPID)	□
Product Patent Expiration Date	□
Compendium of Pharmaceuticals and Specialties listing intention letter	□
Pharmaceutical Advertising Advisory Board (PAAB) approved promotional materials (or draft copy of material submitted to PAAB) or letter requesting waiver.	□
Economic and Epidemiologic Information	□
• Number of patients accessing drugs Pre-NOC and Post-NOC until submitted	□
• Disease prevalence and incidence data, with breakdown where available	□
• BIAs	□
▪ Newfoundland and Labrador	□
▪ Prince Edward Island	□
▪ Nova Scotia	□
▪ New Brunswick	□
▪ Ontario	□
▪ Manitoba	□
▪ Saskatchewan	□
▪ Alberta	□
▪ British Columbia	□
▪ NIHB	□
Supporting Documentation for the BIAs includes:	
▪ documentation of all market research or utilization information used in the BIAs	
▪ copies of documents cited in the BIAs.	□
	□

APPENDIX 7C

Combination Products (Funded Components) Submission Requirements Checklist: Category 1

(Required in hard copy and in electronic format as CD, DVD, or memory stick. See Appendix 7F for electronic submission specifications.)

Signed Cover Letter	□
• Priority Review request and justification (if applying for Priority Review)	□
• The New Indication when submitting a Drug with New Indications.	□
• Justification for not providing a Budget Impact Analysis (BIA) for a specific jurisdiction (if relevant)	
• Confirmation that submitted price is current market price or Confidential Price	□
• Names of primary and backup contacts to be contacted regarding Submission	□
Table of Contents	□
Executive Summary	□
• Supporting references for specified listing when requested by Manufacturer	□
Health Canada NOC or NOC/c (dated and signed)	□
• Letter of Undertaking (if NOC/c).	□
Product Monograph	□
Efficacy, Effectiveness, and Safety Evidence	
• Completed template in hard copy and electronic copy	□
• One clinical study using the Combination Products (Funded Components)	□
Economic and Epidemiologic Information	
• Number of patients accessing Drugs Pre-NOC and Post-NOC until submitted	□
• Disease prevalence and incidence data with breakdown where available	□
• Completed cost tables (found in template)	□
• BIAs provided with the initial Submissions if Priority Review requested based on cost savings	□
▪ Newfoundland and Labrador	□
▪ Prince Edward Island	□
▪ Nova Scotia	□
▪ New Brunswick	□
▪ Ontario	□
▪ Manitoba	□
▪ Saskatchewan	□
▪ Alberta	□
▪ British Columbia	□
▪ NIHB	□

Supporting Documentation for the BIAs include: ▪ Documentation of all market research or utilization information used in BIAs ▪ Copies of documents cited in the BIAs. ▪ Budget Impact Model (for Priority Reviews based on cost savings) ▪ National Budget Impact Model analysis document (for Priority Reviews based on cost savings)	□ □ □ □ □
Pricing and Availability Information • Submitted pricing reported as price per smallest unit to four decimal places • Signed commitment if submitted price is Confidential Price • Method of distribution	□ □ □
Letter Authorizing Unrestricted Sharing of Information	□

Combination Products (funded products) Submission Requirements Checklist: Category 2

(Note: To be provided as a single package twenty (20) Business Days prior to the targeted CDEC meeting.)

CADTH requires only one (1) complete set of Category 2 Submission Requirements in electronic format only (i.e., CD, DVD, or memory stick).

Drug Notification Form (Drug Identification Number Notification Form) for all strengths and dosage forms, dated and signed	□
Certified Product Information Document (CPID)	□
Product Patent Expiration Date	□
Compendium of Pharmaceuticals and Specialties Listing Intention Letter	□
Pharmaceutical Advertising Advisory Board (PAAB)-Approved Promotional Materials (or Draft Copy of Material Submitted to PAAB) or Letter Requesting Waiver	□
Economic and Epidemiologic Information	
• Number of patients accessing Drugs Pre-NOC and Post-NOC until submitted	□
• Disease prevalence and incidence data with required breakdown where available	□
• BIAs (if not provided with Category 1 requirements)	□
▪ Newfoundland and Labrador	□
▪ Prince Edward Island	□
▪ Nova Scotia	□
▪ New Brunswick	□
▪ Ontario	□
▪ Manitoba	□
▪ Saskatchewan	□
▪ Alberta	□
▪ British Columbia	□
▪ NIHB	□
Supporting Documentation for the BIAs includes:	□
▪ Documentation of all market research or utilization information used in BIAs	□
▪ Copies of documents cited in the BIAs.	□

APPENDIX 7D

Resubmission Requirements Checklist

(Required in hard copy and in electronic format as CD, DVD, or memory stick. See Appendix 7F for electronic submission specifications.)

Signed Cover Letter	□
• Justification for Resubmission	□
• Whether CDs/DVDs/memory sticks are included with hard submission	□
• Whether changes to the current Product Monograph are anticipated	□
• Priority Review request and justification (if applying for Priority Review)	□
• Justification for not providing a BIA for a specific jurisdiction (if relevant)	□
• Confirmation that submitted price is current market price or Confidential Price	□
• Names of primary and backup contacts to be contacted regarding Submission.	□
Table of Contents	□
Executive Summary (hard copy and electronic copy)	□
• Supporting references for specified listing when requested by Manufacturer.	□
Product Monograph	
• Indication if and when new Product Monograph may be anticipated	□
New Information	□
• List of all New Information not previously submitted	□
◦ Copies of New Information.	□
• Diagrams following CONSORT reporting standards, documenting flow of patients through studies	□
• Updated tabulated list of published and unpublished studies (Appendix 9)	□
• Search strategies	□
• Signed declaration that all unpublished studies have been disclosed	□
If New Information is new clinical information supporting efficacy:	□
• New randomized controlled trial(s)	□
• New pharmacoeconomic evaluation (3 CDs with copies of executable economic model)	□
• Number of patients accessing drugs pre-NOC and post-NOC until submitted disease prevalence and incidence data with required breakdown, where available	□
• BIAs (Newfoundland and Labrador, Prince Edward Island, Nova Scotia, New Brunswick, Ontario, Manitoba, Saskatchewan, Alberta, British Columbia, Non-insured health benefits)	□
Supporting documentation for the BIAs includes:	
▪ Documentation of all market research information used in BIAs	□
▪ Copies of documents cited in BIAs	□
If New Information is supporting improved safety:	□
• New case control or cohort study(ies)	□

• New pharmacoeconomic evaluation (3 CDs with copies of executable economic model) • Number of patients accessing drugs pre-NOC and post-NOC until submitted • Disease prevalence, and incidence data with required breakdown, where available • BIAs (Newfoundland and Labrador, Prince Edward Island, Nova Scotia, New Brunswick, Ontario, Manitoba, Saskatchewan, Alberta, British Columbia, Non-insured health benefits) Supporting documentation for the BIAs includes: ▪ Documentation of all market research or utilization information used in BIAs ▪ Copies of documents cited in BIAs	□ □ □ □ □ □
If New Information is new cost information: • New pharmacoeconomic evaluation (3 CDs with copies of executable economic model) • Number of patients accessing drugs pre-NOC and post-NOC until submitted (not required for Drugs with New Indication[s]) • Disease prevalence and incidence data with required breakdown where available • BIAs (Newfoundland and Labrador, Prince Edward Island, Nova Scotia, New Brunswick, Ontario, Manitoba, Saskatchewan, Alberta, British Columbia, Non-insured health benefits) Supporting documentation for the BIAs includes: ▪ Documentation of all market research or utilization information used in BIAs ▪ Copies of documents cited in BIAs	□ □ □ □ □ □ □
Note: if Priority Review based on cost is being requested, the following must also be provided: • Budget Impact Model [for Priority Reviews based on cost savings] • National Budget Impact analysis document [for Priority Reviews based on cost savings]	 □ □
Status of confirmatory studies for Resubmissions of Drug with NOC/c **Most recent interim analysis of confirmatory studies for Drug with NOC/c**	 □
Economic and Epidemiologic Information (see above under "New Information")	
Pricing and Availability Information • Submitted pricing reported as price per smallest unit to four decimal places • Signed commitment if submitted price is Confidential Price • Method of distribution.	 □ □ □
Letter Authorizing Unrestricted Sharing of Information	□
Drug Notification Form for all strengths and dosage forms **(Copy of Most Recent Form)**	□
List of Participating Drug Plan Listing Decisions	□

APPENDIX 7E

General Requirements Checklist

Depending on the Submission type, the content is organized in the order outlined in sections 4.2, 4.3, or 4.4 of this document or the content of the Resubmission is organized in the order outlined in section 5.2 of this document.	□
Each section of the Submission is labelled with large tabs.	□
Each file submitted electronically is labelled with the brand name of the drug in the Submission or Resubmission and the type of file. (See Appendix 7F.)	□
The pages are numbered consecutively from the beginning to the end of the Submission or consecutively within each section with clear identification of section and page number. • Category 1 and Category 2 requirements are numbered separately.	□ □
Binders are sturdy and not overfilled (maximum thickness seven [7] centimetres or three [3] inches).	□
Binders are clearly labelled with the name of the Drug, Manufacturer, date, binder x (number) of y (total number of binders).	□
Double-sided pages are used.	□
Submission (including submitted studies) is provided in English.	□
Only Confidential Information is labelled as "Confidential."	□
All required information is included with unpublished studies, under the following headings: • Objective and rationale of study • Intervention • Study population (eligibility criteria, baseline characteristics, and sample size) • Methods (including randomization, blinding, handling of withdrawals/drop-outs, allocation concealment, and outcome measurement) • Results (all beneficial and harmful patient effects, including an itemization of fatal and non-fatal serious adverse events; number of withdrawals and drop-outs with reasons; measure of dispersion such as standard deviation or standard error must be provided for continuous outcomes; numerators and denominators must be provided for dichotomous outcomes) • Data analysis • Conclusions	□ □ □ □ □ □ □ □

APPENDIX 7F: Specifications for Submitting in Electronic Format

When filing the initial Submission or Resubmission with CADTH, Manufacturers must file a hard copy of the complete Submission or Resubmission, along with three (3) copies of the economic model in executable electronic format. When the Submission or Resubmission is deemed complete, the Manufacturer must provide it as described in these Submission Requirements (see Section 4.1.3) and to participating Drug Plans as indicated in Appendix 1 of this document.

Because the file name cannot exceed 64 characters, Manufacturers are invited to use abbreviations for the indication.

When CADTH requests additional information to address the Review Team's needs that arise during the course of a review, Manufacturers can respond by providing it by email or, if the document is very long (e.g., Clinical Study Report), the information can be sent to CADTH as a CD, DVD, or memory stick.

Specifications for Submitting

- The media device used should be a CD or a DVD in a labelled case, or a memory stick in a labelled container.
- Documents must be provided in Microsoft Word or in a PDF format that is unlocked, searchable, and printable. Users must be able to extract information or combine documents.
- Documents must be easily identified and thus labelled as follows:
- Brand name_Indication_document type (e.g., product monograph, Module 2.5, etc.).pdf or doc. The file name must not exceed 64 characters.
- Documents should be organized in three or more CDs or DVDs or in a memory stick, as follows (Note: The order of the documents follows the Submission Requirements in the *Common Drug Review Submission Guidelines for Manufacturers)*:
  - Category 1 submission requirements *excluding* the economic model and related documentation on one CD or DVD or memory stick
  - Economic model and related documentation on one CD or DVD or memory stick
  - Category 2 requirements on one CD or DVD or memory stick
  - Additional, well-labelled CDs or DVDs or memory sticks, if required.

Format for Electronic Files for Submissions

The folders and files reflect the requirements and the order of the requirements for submissions for new drugs, as described in the *Common Drug Review Submission Guidelines for Manufacturers.* Other submissions (e.g., Pre-Notice of Compliance [Pre-NOC] Priority Review submissions) and Resubmissions are required to meet the same format and naming conventions for the electronic files, but follow the order of included information as outlined in the *Common Drug Review Submission Guidelines for Manufacturers* (see checklists in Appendix 7).

Legend


Represents a CD or DVD or memory stick.

Represents one folder.

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


CD or DVD or memory stick #1: Brand Name_Generic Name_Indication_Date — Category

01_Brand Name_Indication_General Information
- 01.01_Brand Name_Signed Cover Letter
- 01.02_Brand Name Table of Contents
- 01.03_Brand Name_Executive Summary
- 01.04_Brand Name_Health Canada NOC or NOC/c
- 01.05_Brand Name_Product Monograph

02_Brand Name_ Indication_Clinical Information

02.01_Brand Name_Health_Canada_Module_2
- 02.01.01_Brand Name_Module 2.5
- 02.01.02_Brand Name_Module 2.7.1
- 02.01.03_Brand Name_Module 2.7.3
- 02.01.04_Brand Name_Module 2.7.4
- 02.01.05_Brand Name_Module 2.7.6

02.02_Brand Name_Indication_Critical Studies

Note 1: Critical studies and all trials discussed in the clinical evidence portion of the submission should be included in this folder (Brand Name_ Health Canada_Module 2). Each trial should be a separate document. When feasible, the trial should be numbered with the same number as listed in the reference list, and the name should be short and concise. For example:
- 02.02.01_Smith et al.CMAJ.2007.pdf
- 02.02.02_Wong.BMJ.2008.pdf
- 02.02.03_manufacturer.unpublished.2010.pdf
- 02.02.04_Brown et al.poster.2010.pdf
- 02.02.05_Lee.[abstract].J Cardiology.2010.pdf

02.03_Brand Name_Indication_CONSORT

(*Note:* It may be a CONSORT-like diagram.)
- 02.03.01_Brand Name_ CONSORT diagram (Study x)
- 02.03.02_Brand Name_ CONSORT diagram (Study y)

Etc.

- 02.04_Brand Name_Indication_New data after NDS
  (See Note 1, above, for recommendation on labelling references.)
  - 02.04.01_Smith et al.CMAJ.2007.pdf
- 02.05_Brand Name_Indication_Editorial articles and errata
  (See Note 1, above, for recommendation on labelling references.)
  - 02.05.01_Smith et al.CMAJ.2007.pdf
- 02.06_Brand Name_Indication_References supporting outcome measures
  (See Note 1, above, for recommendation on labelling references.)
  - 02.06.01_Smith et al.CMAJ.2007.pdf
- 02.07_Brand Name_Indication_Table-Published_Unpublished Studies
  (Note: This is Appendix 9.)
  - Brand Name_Table of Studies
- 02.08_Brand Name_Indication_Disclosure-unpublished studies
  - Brand Name_Signed Disclosure of Unpublished Studies
- 02.09_Brand Name_Indication_Search Strategies
  - Brand Name_Search strategy

03_Brand Name_Indication_Pharmacoeconomic Evaluation
- 03.01_ Brand Name_Pharmacoeconomic Evaluation

04_Brand Name_Indication_Epidemiologic Information
- 04.01_Brand Name_Patients on Drugs Pre-NOC and Post-NOC
- 04.02_Brand Name_Disease Prevalence and Incidence

05_Brand Name_Indication_BIAs
(Budget Impact Analyses [BIAs] are required if the submission is for Priority Review based on cost)

- 05.01_Brand Name_BIAs
  BIAs should be labelled by jurisdiction (Newfoundland and Labrador[NL], Prince Edward Island [PE], Nova Scotia [NS], New Brunswick [NB], Ontario [ON], Manitoba [MN], Saskatchewan [SK], Alberta [AB], British Columbia [BC], Non-Insured Health Benefits [NIHB]), for example:
  - 05.01.01_Brand Name_BIA_BC
  - 05.01.02_Brand Name_BIA_ AB

  etc.
- 05.02_Brand Name_Indication_Supporting Documentation for BIAs
- 05.03_Brand Name_Indication_Price-Supply-Information Sharing
  - 05.03.01_Brand Name_Pricing and Availability Information
- 05.03.03_Brand Name_Letter–Information Sharing

CD or DVD or memory stick #2: Brand Name_Generic Name_Indication_Economic Model

- 01_Brand Name_Indication_Economic Model and Documentation
  - 01.01_Brand Name_Economic Model
  - 01.01_Brand Name_Economic Documentation

CD or DVD or memory stick #3: Brand Name_Generic Name_Indication_Category 2

- 01_Brand Name_Indication_Additional Regulatory and Other Information
  - 01.01_Brand Name_Ability to Supply
  - 01.02_Brand Name_Drug Notification Forms
  - 01.03_Brand Name_Certified Product Information Document
  - 01.04_Brand Name_Product Patent Expiration Date
  - 01.05_Brand Name_CPS Listing Intention Letter
  - 01.06_Brand Name_PAAB-Approved Promotional Material

- 02_Brand Name_Indication_Epidemiologic Information
  - 02.01_Brand Name_Patients on Drug Pre-NOC and Post-NOC
  - 02.02_Brand Name_Disease Prevalence and Incidence

- 03_Brand Name_Indication_BIAs (if not submitted as Category 1 requirement)

BIAs labelled by jurisdiction (Newfoundland and Labrador[NL], Prince Edward Island [PE], Nova Scotia [NS], New Brunswick [NB], Ontario [ON], Manitoba [MN], Saskatchewan [SK], Alberta [AB], British Columbia [BC], Non-Insured Health Benefits [NIHB]) , for example:

- 03.01_Brand Name_Indication_BIAs
  - 03.01.01_Brand Name_BIA BC
  - 03.01.02_Brand Name_BIA AB

  etc.
- 03.02_Brand Name_Indication_Documentation for BIAs

CD or DVD or memory stick #4: Brand Name_Generic Name_Indication_Additional Information

(To be determined by manufacturer on a case by case basis, depending on additional information that is being provided. The same naming conventions should be followed as above.)

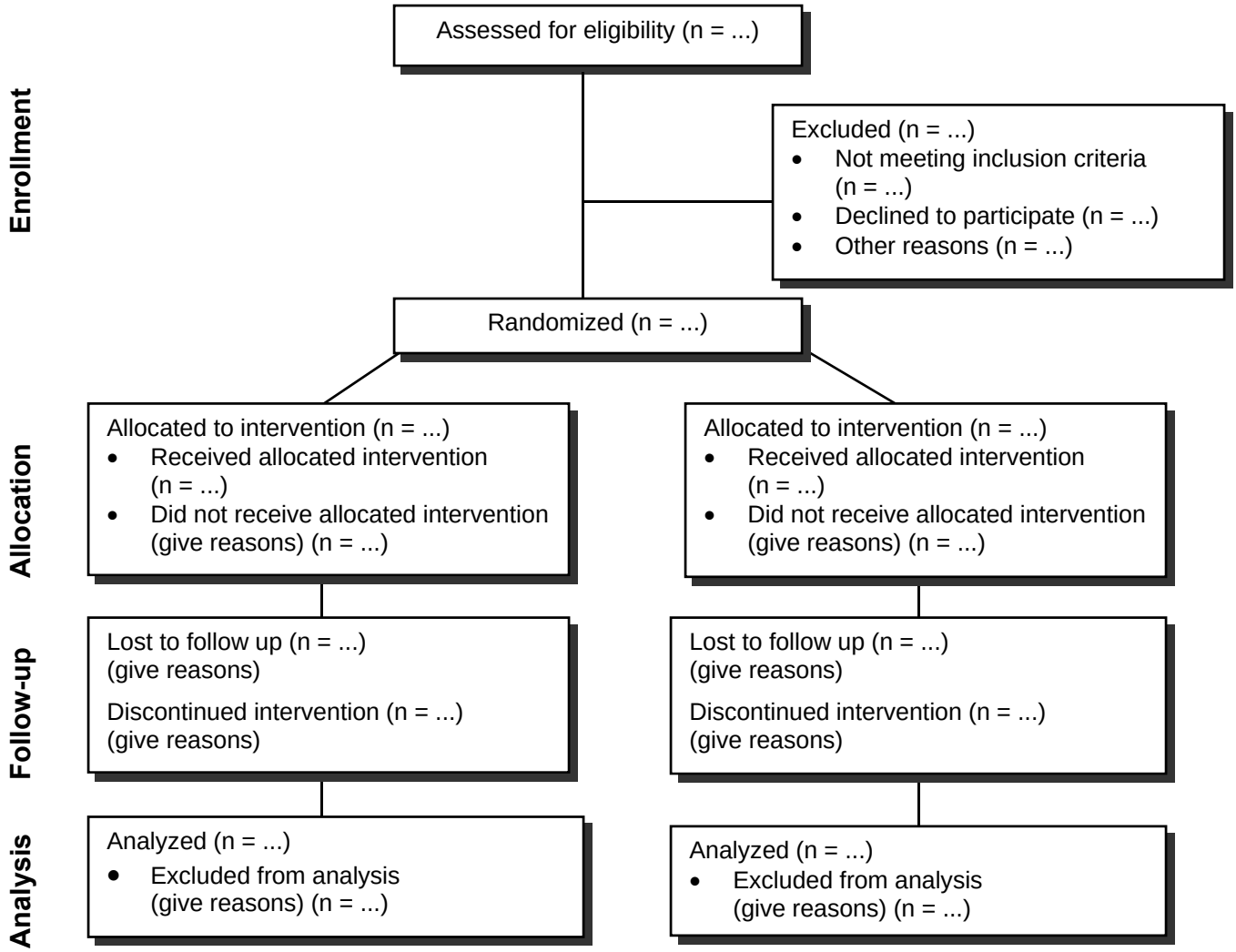
- 01_Brand Name_Indication_:
  - 01.01_Brand Name_Indication_xxxxx
  - 01.02_Brand Name_Indication_zzzzz

APPENDIX 8: CONSORT Reporting Standard for Documenting Patient Flow

(Note: This is an example of the type of information that is required for the CDR process. It can be provided in a different format as long as all of the information shown in the flowchart below is provided.)

CONSORT Flowchart

Flow Diagram of the progress through the phases of a randomized trial (i.e., enrollment, intervention allocation, follow-up, and data analysis)



For Reference: Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *PloS Med* [Internet]. 2010 [cited 2010 Apr 21];7(3):e1000251. Available from: http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000251

APPENDIX 9: Table Template for Listing Canadian and International Published and Unpublished Studies

(Note: An example is included to illustrate the level of detail required. This table may be expanded. A copy of this table is required in hard copy and as an electronic copy (Microsoft Word format on CD). All parts of the template must be completed as per instructions in footnotes.)

List of Canadian and International Published and Unpublished Studies for [Name of Drug in Submission]

Study ID*	Alternate Study IDs	Sponsor†	Description‡	Phase**	Start Date	End Date††	Abstracts and Publications‡‡	Location in Submission*** and PDF§
List of All Completed Published and Unpublished Studies INCLUDED in Submission†††								
AB12345	BONE, B-21	Bones Manuf Inc.	Efficacy of Drug A in reducing hip fractures in adults with osteoporosis. (title) A two-year randomized, double blind, placebo-controlled, multi-centre trial of 552 patients to assess the efficacy of drug A in reducing hip fractures in adult patients with osteoporosis; 50 mg given daily	3	February 2005	June 2007	Jones, F. Drug A: efficacy results from Phase 2/3 clinical trials [abstract]. Association for Research in Osteoporosis Annual Meeting. 2005 April 25-26; New Orleans. Abstract No. 23.	Efficacy, Effectiveness & Safety Evidence: p. 72 of 417
List of All Completed Published and Unpublished Studies for All Indications NOT INCLUDED in Submission‡‡‡								
List of All Ongoing Studies								

*Study ID: Provide the combination of numbers and/or letters assigned by the sponsoring organization to identify the study.
†Sponsor = Sponsor of the study.
‡Briefly describe the study design [e.g., randomized, blinded (double or single), controlled, open label, extension, long-term safety, etc.], number of patients, objective(s), description of each treatment arm (drugs and doses); outcomes specified in protocol; duration of treatment; condition or disease; the summary/description should be concise and brief. Include study title. **All information, requested in this bullet, must be included**.
**Indicate if Phase 2, 3, or 4 (do not include Phase 1 studies).
††Indicate when the study is scheduled to end or the date completed or stopped.
‡‡Provide complete citations of all abstracts or publications (e.g., published report on interim findings) related to the included unpublished studies. Include editorials and errata related to included published studies.
***Indicate the name of the tab under which the included study is located.
§ When available, insert a PDF copy of the abstract or publication.
†††Include Phase 3 studies described in the Common Technical Document.
‡‡‡Contact the CDR Directorate for guidance if Drug has been available for more than 10 years in Canada or internationally.

APPENDIX 10: Letter 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 of Manufacturer of Product]

APPENDIX 11: Letter Template for Confirming Ability to Supply

(Note: This template can be used for all Submissions, including Pre-NOC Submissions. Confirming ability to supply is a Category 2 requirement for all Submissions.)

[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]

i) will supply the Drug at the submitted price, as provided elsewhere in this Submission, to all CDR participating Drug Plans;
ii) is currently able (i.e., at the time of filing this submission) to supply the above drug product at the submitted price in a quantity sufficient to meet the anticipated national demands for this product.

[Signature]

[Name and Title of Senior Company Official of Manufacturer of Product]

APPENDIX 12: Letter Template for Authorizing Unrestricted Sharing of Information

(Note: 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.)

[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 of Manufacturer of Product]

APPENDIX 13: 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 information has been provided to CADTH for the stated Pre-NOC Submission.)

[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 [or Notice of Compliance with Conditions].

This letter confirms that all material filed with CADTH for this Pre-NOC Submission is finalized.

[Signature]

[Name and Title of Senior Company Official of Manufacturer of Product]

APPENDIX 14(a): Letter of Authorization (Pre-NOC Submissions Only)

[Drug Submission Sponsor]
[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

and

Bureau Director [Bureau] Therapeutic Products Directorate Health Products and Food Branch Health Canada	or	Director, Office of Regulatory Affairs Biologics and Genetic Therapies Directorate Health Products and Food Branch Health Canada

Dear

Re: [Product Name], [Health Canada Submission No.]

This letter serves to authorize the Canadian Agency for Drugs and Technologies in Health (CADTH) to request that Health Canada provide, for the CDR review, information submitted by [submission sponsor] to Health Canada regarding the above-noted drug submission. This authorization shall only apply to information submitted up to and including the date of the decision by Health Canada regarding market authorization.

This letter also serves to authorize Health Canada to release the requested information set out above, with the restrictions noted, to CADTH for the CDR review. Health Canada may also respond to inquiries from CADTH regarding the information provided pursuant to this letter of authorization. Please note that any reports resulting from the information submitted by your organization prepared by, or on behalf of, Health Canada in consideration of your submission, may also be shared with CADTH subject to any applicable restrictions.

We request that any information or document released to CADTH pursuant to this letter of authorization shall be deemed to constitute "Confidential Information" pursuant to the Procedures for Common Drug Review adopted by CADTH, and shall be treated as such by CADTH.

[Signature]

[Name and title of authorizing officer]
[Submission manufacturer corporate name]

APPENDIX 14(b): Information to Be Sent to CADTH (Pre-NOC Submissions Only)

(Note: This document is to be submitted to CADTH by the Manufacturer after completion by Health Canada.)

Drug Name		
Brand Name	**Active Ingredient**	
Manufacturer		
Manufacturer's contact for CADTH (for CDR review)		
Name:	Telephone No.:	
Potential indication(s) being considered by HC		
Anticipated date to start Product Monograph negotiations:		
Year:	Month:	Day:
Regulatory Project Manager at HC (to serve as CADTH's contact person for the CDR review of submission)		
Name:	Telephone No.::	
HC reviewer (or Division Manager) contact information		
Name:	Telephone No.:	

Documents Included		
Clarifaxes and associated responses		☐
Meeting minutes from any meetings (including teleconferences) held with respect to the product, both prior to and after the submission being filed.		☐
Proposed Product Monograph		☐
Copy of authorization letter from manufacturer		☐
Was a statistical review done by the Office of Science?	**Yes** ☐	**No** ☐
Was the sponsor requested to perform an additional statistical analysis?	**Yes** ☐	**No** ☐
Were Periodic Safety Update Reports requested by and provided to HC?	**Yes** ☐	**No** ☐
If so indicate date most recent version.	**Date**:	

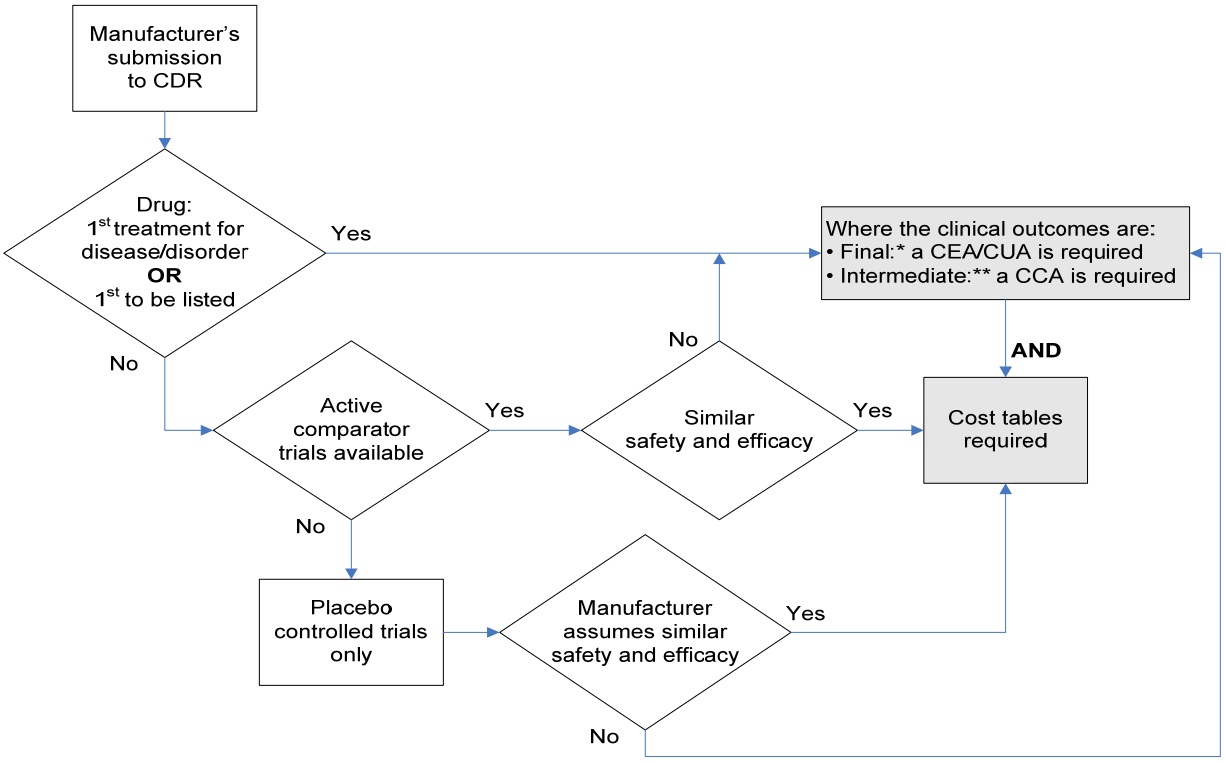
APPENDIX 15: Guidelines for the Type of Economic Analysis to Be Submitted

An appropriate pharmacoeconomic evaluation is required for all Submissions. If there are subgroups that may benefit from the Drug or specific reimbursement criteria, requested by the Manufacturer, additional analyses should be provided. This appendix provides guidance for the type of economic analysis to submit to the CDR. Users of this document should also refer to Economic and Epidemiologic Information in sections 4.2.1(g), 4.3.1(h) and 5.2.2(g). For methodological details, see the CADTH document, *Guidelines for the Economic Evaluation of Health Technologies: Canada*.

Based on the type of drug being submitted and its expected place in therapy, specific guidance is provided in the following information.

Where it is unclear which type of economic analysis should be submitted, the Manufacturer may contact CADTH. CADTH will be able to provide clarification based only on the information provided by the Manufacturer, which should include the name of the Drug, indication, dosage, pharmacologic classification, clinical trial information, and cost.

Figure 1: Summary of the Guidelines for the Type of Economic Analysis to Submit



CEA = cost-effectiveness analysis; CCA = cost-consequence analysis; CUA = cost-utility analysis;
* Final Clinical Outcome = an event that is relevant and noticeable to patients;
**Intermediate Clinical Outcome = includes subjective clinical measures where extrapolation of health benefits to life-years or quality-adjusted life-years (QALYs) is more difficult (migraine pain score, urinary symptom scale), non-clinical endpoints, or surrogate endpoints.

1 The Drug is the First Available for Treatment of the Disorder or Disease, or the First to be Listed by Participating Drug Plans

Drugs that fall under this category include, but are not limited to: Drugs indicated for the treatment of diseases or disorders for which there are currently no drugs approved in Canada or Drugs that establish a new therapeutic class for the treatment of a disease or disorder; Drugs that consist of new molecules; Drugs with new mechanisms of action; and Drugs that meet the requirements for Subsequent Entry Biologics based on guidance from Health Canada.

Table 1: Guidelines for Economic Analyses to be Submitted if the Drug Is the First Available Treatment

Clinical Outcomes	Final	Intermediate
Primary analysis	CEA/CUA	CEA/CUA CCA
Acceptable pharmacoeconomic outcomes	- Cost per LYG - Cost per QALY - Cost per event avoided (section 1.1.1 of this appendix)	CCA: - Cost analysis - Cost per event avoided - Cost per additional response *Only* if surrogate has been shown to be a valid surrogate for a final outcome: - Cost per QALY or LYG (section 1.2.1 of this appendix)
Comparator	Standard or current care (section 1.1.2 or 1.2.2 of this appendix)	
Details of cost estimates	Price comparison table and health care cost tables (section 1.1.3 or 1.2.3 of this appendix)	

CEA = cost-effectiveness analysis; CCA = cost-consequence analysis; CUA = cost-utility analysis; LYG = life-year gained; QALY = quality-adjusted life-year.

The preferred clinical outcomes for the CDR are Final Clinical Outcomes, which are described in section 1.1 of this appendix. If Final and Intermediate Outcomes are available, the submitted analysis should be based on Final Clinical Outcomes. Where possible, the Manufacturer should provide clinical evidence detailing the implications of the submitted treatment on Final Clinical Outcomes. Where this information is not available, surrogate outcomes shown to be valid surrogates for Final Clinical Outcomes may be used. If data are not available to support the relationship between surrogate and Final Clinical Outcomes, a cost-consequence should be provided.

1.1 Final Clinical Outcomes

A Final Clinical Outcome is defined as an event that is relevant and noticeable to patients. Outcomes may include:

- survival (overall)
- non-subjective clinical outcome measures, or disease or condition-related events that enable health benefits to be expressed in life-years, QALYs, or events (e.g., myocardial infarction, stroke, or fracture).

1.1.1 Primary Type of Analysis

The primary type of analysis should be presented as a cost-utility analysis or cost-effectiveness, reporting:

- cost per life-year gained or cost per QALY gained
- cost per clinical event avoided (only for "non-subjective clinical outcome measures" when extrapolation to life-years or QALYs is inappropriate).

Other analyses may be provided in the appendix of the Manufacturer's Submission. CADTH will assess whether the additional information is relevant and whether the details will be included in the CDR Pharmacoeconomic Report.

1.1.2 Comparator

In all cases, the new therapy should be compared with the accepted therapy (existing practice), where accepted treatment would either be the single most prevalent clinical practice (if there is one that is dominant). Where generic versions of the accepted therapies exist, the price of the generic drug should be used. All other reasonable alternative therapies should be at least discussed in the report.

See the CADTH document, *Guidelines for the Economic Evaluation of Health Technologies: Canada* for further guidance.

1.1.3 Requirements for Cost Data

Companies should submit a price comparison table (Table 3 in this appendix) and cost tables (Tables 4 and 5 in this appendix) outlining all appropriate costs, identifying source, and assumptions for the costs included in each category.

1.2 Intermediate Clinical Outcomes

These include subjective clinical measures where extrapolation of health benefits to life-years or QALYs is more difficult (migraine pain score, urinary symptom scale), non-clinical endpoints, or surrogate endpoints. A surrogate endpoint is an endpoint that is intended to relate to a clinically important outcome but does not in itself measure a clinical benefit. Surrogate endpoints may be used as primary endpoints when appropriate (when the surrogate is reasonably likely or well known to predict clinical outcome) (Health Canada, http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e8_e.html).

1.2.1 Primary Type of Analysis

The primary type of analysis should be presented as a cost-consequence analysis. Since the clinical data will be taken from the CDR Clinical Review for the Submission under review, only the cost tables will need to be completed (See Suggested Format of Cost Information in this appendix).

Where appropriate, companies may choose to present the analysis as a *cost per event avoided or cost per additional response*. Companies should present a cost per QALY gained (or cost per life-year gained) analysis only if the surrogate endpoint has been shown to be a valid surrogate for true clinical outcomes. In such a case, the company should present, in a succinct fashion, the quantitative evidence justifying the surrogate as a valid predictor of clinical outcomes. Other analyses may be provided in the appendix of the Manufacturer's Submission and referred to in the main text of the

report. CADTH will assess whether the additional information is relevant and whether the details will be included in the *CDR Pharmacoeconomic Report*.

1.2.2 Comparator

In all cases, the new therapy should be compared against current practice (See Final Clinical Outcomes, Comparator section in this appendix).

1.2.3 Requirements for Cost Data

Companies should submit a price comparison table (Table 3 in this appendix) and cost tables (Tables 4 and 5 in this appendix) outlining all appropriate costs and identifying source and assumptions for the costs included in each category.

1.3 Suggested Content for Submission

Companies should include the following information when submitting an economic evaluation for CDR review:

- Description of the study treatment
- Description of, and justification of, comparator(s) (i.e., reflects current management)
- Description of indication or treatment population
- Perspective
- Time horizon and justification
- Discount rates and justification (if applicable)
- Target audience
- Type of economic analysis and justification
- Appropriate and clear description of research methodology
- Clear description of data sources: effectiveness, cost and resource use, and other data
- Inclusion of pertinent outcome parameters (if applicable)
- Description of any assumptions used in the analysis
- Identification and definition of the key cost drivers
- Report of total and incremental costs and effects
- Description, justification, and comprehensive reporting of sensitivity analyses (if applicable)
- Discussion of limitations
- Discussion of equity considerations
- Discussion of transferability of results across different jurisdictions.

For more detailed information on reporting structure, companies should refer to the CADTH document, *Guidelines for the Economic Evaluation of Health Technologies: Canada* (3rd edition, 2006).

2 The Drug Is Not the First Available Treatment for the Disorder or Disease

Drugs that fall under this category include Drugs that largely duplicate the action of existing drugs (i.e., Drugs in an established class with a similar mechanism of action and therapeutic use) and combination products (for which all constituent Drugs are funded). Table 2 shows the analysis required.

<table>
<tr><th colspan="4">Table 2: Guidelines for Economic Analyses Conducted for Subsequent Drugs Available for the Disorder or Disease</th></tr>
<tr><td colspan="4">Submitted Drug: Drug Is Not the First Available for the Disorder or Disease</td></tr>
<tr><td colspan="4">Is the Drug one in an established class (i.e. Drugs with same mechanism of action and therapeutic use)</td></tr>
<tr><td>No</td><td colspan="3">Follow process for first available treatment
(section 1 of this appendix)</td></tr>
<tr><td rowspan="6">Yes</td><td colspan="3">Trial(s) versus other available treatments?</td></tr>
<tr><td rowspan="3">Yes</td><td colspan="2">Results from trial(s) show no difference in efficacy and safety?</td></tr>
<tr><td>Yes</td><td>Complete cost tables
(section 3 of this appendix)</td></tr>
<tr><td>No</td><td>Follow process for first available treatment
(section 1 of this appendix)</td></tr>
<tr><td rowspan="3">No</td><td colspan="2">Manufacturer assumes similar clinical benefits of Drug*?</td></tr>
<tr><td>Yes</td><td>Complete cost tables
(section 3 of this appendix)</td></tr>
<tr><td>No</td><td>Follow process for first available treatment
(section 1 of this appendix)</td></tr>
</table>

*This might be supported through indirect comparison.

If other available treatments are listed as benefits by any of the participating publicly funded F/P/T Drug Plans in Canada, the Manufacturer needs to indicate whether a randomized trial has been conducted comparing the new therapy with either the first available drug or other available drugs for the disorder or disease.

2.1 Head-to-head trials have been conducted versus other available drugs*

**Other available drugs for the disorder or disease that are listed as benefits by any of the participating Drug Plans*

Do the results of the trial(s) show no difference in safety and efficacy?
"No difference in safety and efficacy" is defined as the lack of any *statistically significant differences* between the intervention and alternatives. This decision should be based on a high quality clinical assessment of the intervention.

Beyond treatment effects, the submitted Drug may differ from alternatives in terms of compliance or convenience of use (e.g., due to less frequent drug administration). These differences should only be

considered as relevant for claiming clinical benefits if they have been linked to changes in clinically meaningful outcomes.
(Note: Inappropriate assumptions of clinical equivalence compared with existing available drugs for treatment of this disease or disorder may compromise the ability to fully review the submitted Drug.)

2.1.1 Results from the head-to-head trial(s) show no difference in safety and efficacy (non-inferiority or non-superiority)

Requirements for Cost Data — Companies should submit a price comparison table (Table 3 of this appendix) and cost tables (Tables 4 and 5 of this appendix) outlining all appropriate costs, identifying source, and assumptions for the costs included in each category.

2.1.2 Results from the head-to-head trial show difference(s) in safety and/or efficacy

Follow submission process for first available drug (section 1 of this appendix).

2.2 No head-to-head trial(s) have been conducted versus another available drug*

**Other available drugs for the treatment or management of the disorder or disease that are listed as benefits by any of the participating Drug Plans*

2.2.1 Manufacturer assumes Drug provides similar clinical benefits versus other Drugs in class

Requirements for Cost Data — Companies should submit a price comparison table (Table 3 of this appendix) and cost tables (Tables 4 and 5 of this appendix) outlining all appropriate costs, identifying source, and assumptions for the costs included in each category.

2.2.2 Manufacturer assumes Drug provides different clinical benefits versus other Drugs in class

Where the Manufacturer is assuming different clinical benefit (efficacy or effectiveness or safety) of the submitted Drug compared with other drugs in the class, the evidence to support these claims should be provided in detail. This may include: a description of the indirect comparison conducted and the methods employed; reference to other studies that may provide information on clinical benefits other than efficacy and safety; or post- marketing data that provides information on longer-term safety.

Follow the submission process of first available drug (see section 1 of this appendix).

2.3 Suggested Content for Submission

Companies should include the following information for CDR review when submitting economic information in support of a drug for which similar drugs are currently available:

- Description of the study treatment
- Description of, and justification of, comparator(s)
- Description of indication or treatment population
- Perspective

- Time horizon considered in cost table(s) and justification
- Discount rates and justification (if considering time horizons beyond one year)
- Justification for approach to economic submission [cost table(s)] — this may include reference to specific studies or sections in the submission binder
- Clear description of data sources: effectiveness/efficacy, safety, cost and resource use, and other data
- Appropriate and clear description of research methodology (if applicable)
- Description of any assumptions used in the analysis
- Cost table(s) (Tables 3, 4, and 5 of this appendix)
- Description, justification, and reporting of sensitivity analyses (if applicable)
- Discussion of limitations.

3 Suggested Format of Cost Information

Tables 3 to 5 are suggested possible approaches for reporting cost data. Manufacturers are strongly urged to consider all potentially relevant costs that may be applicable to their Drug; the cost components listed in the sample tables by no means reflect a comprehensive list of all possible costs. Also, Manufacturers may provide tables that are more specific to their submitted Drug. The following tables are examples intended to assist those submitting economic information.

Table 3: Price Comparison Table

Column 1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7	Column 8	Column 9
Drug	**Strength**	**Form**	**List Price Per Unit (Specify) ($)**	**Average Daily Use**	**Average Daily Drug Cost Per Patient**	**Typical Annual Drug Cost***	**Range of Plausible Costs**	**Extra Columns May Include: Daily Pill Burden, Daily Frequency of Use**
Submitted Drug	XX mg	Tablet or Caplet	$Y	Z mg daily, twice daily, etc.	$A	(Consider actual market use of Drug)	(Consider other patient weights, possible wastage scenarios)	
Comparator 1								
Comparator 2								
Comparator x (previous standard of care)								

*Where the typical duration of treatment is less than one year, the typical cost for a full course of treatment should be considered.

(Note: Data sources and assumptions must be clearly stated by the Manufacturer. As necessary, it is recommended that the company include sections detailing the calculations resulting in the value reported in each of these boxes.)

Included within this table should be a detailed comparison of cost for the submitted Drug with all other available drugs for the treatment of the disease or disorder (if applicable) and with any previous Drugs that were considered standard of care.

A description of the submitted Drug and relevant comparators must be provided in columns 1 through 3. The list price of the treatment per unit and the intended dosing and use should be described in columns 4 to 6. In addition, the typical price of each Drug, as used in clinical practice, should also be addressed in this table. "Typical Annual Drug Cost" should account for the actual doses used, wastage (where partial vials cannot be re-used), etc. The components included in this figure should be clearly detailed, and details of how this number was derived should be provided. These details should be provided in a footnote to this table or, if necessary, in an appendix to the pharmacoeconomic submission. Factors that may affect the cost of the treatment should be detailed in column 8, "Range of Plausible Costs." These factors might include patient weight, possible wastage, and treatment resistance. Additional columns may be included if necessary; justification must be provided for the inclusion of additional information. For example (column 9), where complex dosing or treatment regimens are being considered, the number of pills per day, or the frequency of use may be relevant.

Table 4: Direct Health Care Costs						
Category	**Submitted Drug**	**Comparator A**	**Comparator B**	**(Other Appropriate Comparator)**	**Time Frame***	**Data Source(s)**
Drug — List price†						
Drug — Typical cost†						
Costs incurred during treatment						
Administration of Drug (specify clinic time, outpatient visit, supplies, where relevant)						
Monitoring						
Other costs induced through use of the Drug (specify treatment of adverse events or complications, concomitant drugs, etc.)						
Costs that may be impacted by treatment (specify surgery, in-hospital stay)						
Costs incurred beyond treatment						
Medical costs (specify cost of treating disease, complications with treatment)						

* Specify time frame: monthly, annual, or lifetime, etc.
†As detailed in Table 3 of this appendix.

Table 4 of this appendix details the direct health care costs associated with the submitted Drug. For each category, the costs provided should be reported as *mean total cost per patient* (i.e., taking into account the frequency of an event and its cost).

(Note: Data sources and assumptions must be clearly stated by the Manufacturer. As necessary, it is recommended that the company include sections detailing the calculations resulting in each of these boxes.)

Relevant cost items should be detailed in the rows, under the appropriate heading — examples have been provided of possible cost items. Other comparators may be included in this table; include columns as necessary.

Costs incurred during treatment
The costs to be included under this subheading are those incurred by individuals during, for instance, the course of the clinical trial. These might include the cost of administering the Drug, such as clinic time, visits to the physician, and supplies. Induced costs of treatment may include items such as additional time required to monitor patients receiving treatment, lab tests, treatment-related complications (which may include the need for additional Drugs, outpatient visits, hospitalizations etc.). Costs that may be impacted by the use of a Drug for a condition should also be included in this subsection, which might include the treatment of disease-related complications, hospitalizations, and emergency room visits. Where the costs have not been collected alongside the clinical trial, it should be indicated that the costs were derived by the economic model, and specific sources and assumptions should be stated in the last column.

Costs incurred beyond treatment
Based on extrapolation beyond the clinical trial, these are the expected costs for patients receiving the submitted Drug and appropriate comparators during the specified, extended time horizon. This would include the costs of complications caused or prevented by the administration of the New Drug. These costs tend to be more important when performing full economic evaluations.

Table 5: Non-Health Care Resources and Costs						
Category	**Submitted Drug**	**Comparator A**	**Comparator B**	**Other Appropriate Comparator**	**Time Frame***	**Data Source(s)**
Patient's time (total)						
Treatment time						
Lost productivity						
Caregiver time						
Out-of-pocket costs (total)						
(Specify individual items: travel expenses, child care, modifications to home)						

* Specify time frame: monthly, annual or lifetime, etc.

Table 5 of this appendix details the non-health care resources and costs associated with the submitted treatment compared with the appropriate comparators. Where non-health care costs are relevant in the economic evaluation, this table *must* be completed.

(Note: Data sources and assumptions must be clearly stated by Manufacturer. As necessary, it is recommended that the company include sections detailing the calculations resulting in each of these boxes. Where assumptions or modelling have been conducted to determine the estimates for this table, the validation process for these estimates must be described and results of the validation reported.)

Cells should be completed with respect to the expected cost for each item. The costs are derived by the expected number of hours spent multiplied by the wage or cost per hour. These data should be reported separately, and the sources of this information should be presented clearly.

Patient's time should be reported in terms of the time spent receiving medical care and the lost productive time due to the disease or disability, multiplied by the mean wage or expected cost per hour. Patient and caregiver time must be converted to costs. The values used for this calculation must be provided. Calculations should be provided if the estimate is not transparent. The patient's, or caregiver's, out-of-pocket costs should be detailed. These items might include travel expenses, child care, or modifications to the home.

APPENDIX 16: Template to be Completed by Manufacturer for Combination Products (Funded Components)

(Must be submitted in hard copy and electronic copy — WORD document on CD/DVD or memory stick)

A. RATIONALE FOR THE COMBINATION

Summarize "bottom line" in this box (to be completed by CDR Reviewer).

Manufacturer's Rationale for the Combination (not to exceed two [2] pages of 11-point font)
The required information or evidence must be succinct and entered directly into the template. References must be provided and are to be included in a list of references at the end of the template.

The required information or evidence in this section includes:
- the therapeutic rationale for the combination
- the pharmacological rationale for the combination.

CDR Reviewer Comments Regarding the Rationale for the Combination

To be completed by CDR Reviewers.

B. BIOEQUIVALENCE

Summarize "bottom line" in this box (to be completed by CDR Reviewer).

Manufacturer-Submitted Information Showing Bioequivalence

The required information or evidence must be succinct and entered directly into the template. References must be provided and are to be included in a list of references at the end of the template.

The required information or evidence in this section includes:

- Evidence of bioequivalence of the combination with the individual components.
- A copy of Health Canada Reviewers' Report (also called Pharmaceutical Safety and Efficacy Assessment or the Comprehensive Summary – Bioequivalence [CS-BE]).
- A verbatim quotation from the Health Canada Reviewers' Report regarding the conclusions on bioequivalence.
- A statement indicating whether the individual components have uncomplicated or complicated and variable pharmacokinetic characteristics.
- Evidence that the pharmacokinetic properties (e.g., absorption) of the combination are similar to those of the individual components.

Table 1: Bioequivalence Profile for Combination Products[*†]

Parameter	Component A as Combination AB	Component A as A + B[‡]	Component B as Combination AB	Component B as A + B[‡]
AUC (0-T) • Mean • Standard deviation • Coefficient of variance • Ratio of relative means • 90% confidence interval				
Cmax • Mean • Standard deviation • Coefficient of variance • Ratio of relative means • 90% confidence interval				
Tmax • Mean • Standard deviation • Coefficient of variance				

[*]Add columns to match number of components.
†In accordance with current Health Canada bioequivalence standards and data requirements.
[‡]Component A plus Component B, given concurrently.

CDR Reviewer Comments Regarding Bioequivalence

To be completed by CDR Reviewers.

C. PLACE IN THERAPY

Summarize “bottom line” in this box (to be completed by CDR Reviewer).

Manufacturer-Submitted Information Regarding Place in Therapy (not to exceed two [2] pages of 11-point font)
The required information or evidence must be succinct and entered directly into the template. References must be provided and are to be included in a list of references at the end of the template.

The required information or evidence in this section should include:

- Would the components be the drugs of choice as separate medicines?
- Does the combination contain the most commonly prescribed doses of the individual components?
- Should this combination be used for initiating therapy?
- Titration issues (is therapy initiated with the combination or is a switch to the combination necessary after titration, lack of ability to titrate doses due to limited availability of strengths combination.)
- How likely are dose changes?
- Will increasing the dose of one component result in an unnecessary dose increase in the other component?
- Does the use of the combination overcome any issues or problems related to the administration of the components individually?

CDR Reviewer Comments Regarding Place in Therapy

To be completed by CDR Reviewers.

D. HARMS INFORMATION

Summarize "bottom line" in this box (to be completed by CDR Reviewer).

Manufacturer-Submitted Information Regarding Harms

The required information or evidence must be succinct and entered directly into the template. References must be provided and are to be included in a list of references at the end of the template.

The required information or evidence in this section includes:

- Information about the types of adverse events and their rates for the Combination Product (Funded Components) the components and appropriate comparators.

CDR Reviewer Comments Regarding Harms Information

To be completed by CDR Reviewers.

E. PHARMACOECONOMIC EVALUATION

Summarize "bottom line" in this box (to be completed by CDR Reviewer).

Manufacturer-Submitted Cost Information
The required information or evidence must be succinct and entered directly into the template. Sources of price information must be provided and are to be included as footnotes below the tables.

- Provide price of the Combination Products (Funded Components) (price for all strengths per smallest unit to four decimal places; price for different strengths if applicable) and its daily cost compared with the price of individual components.

Table 2: Cost Comparison of Combination Products (Funded Components) and Individual Components

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Use	Daily Drug Cost ($)
FDC generic name (Brand name)	**A mg/B mg/...Z mg**		**$A/B/…/Z**		**$FDC**
Individual component A (brand and generics)	A mg		$A		$ daily A
Individual component B (brand and generics)	B mg		$B		$ daily B
Individual component up to Z, if applicable (brand and generics)	Z mg		$Z		$ daily Z
Total (A+B+…+Z)					**$ Total of Individual Components**

FDC = Combination Product (Funded Components)

- Include any relevant information on patent expiration for the individual components as a footnote to the table.
- Provide source and where applicable, indicate if the price is a Confidential Price submitted by the Manufacturer.
- Summarize cost differences and potential cost savings of the Combination Products (Funded Components) compared with individual components.
  - Summary of potential cost savings based on Table 1.
  - Quantify the potential daily savings or price difference of the Combination Products (Funded Components) compared with the price of individual components together; provide a range on the cost difference or daily savings.

Cost Comparison Table

A list of prices for all appropriate comparators. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to Drugs, but may be devices or procedures. Costs are Manufacturer list prices, unless otherwise specified.

- List comparators alphabetically by generic name.

Table 3: Cost Comparison Table

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Use	Average Daily Drug Cost ($)
A/B/…/Z (Combination Products [Funded Component] brand)					
Comparators					

Note: Where applicable, indicate if price is a Confidential Price submitted by the Manufacturer. Provide sources for cost information and dosage information.

CDR Reviewer Comments Regarding Cost Information

To be completed by CDR Reviewers.

F. CURRENT PATENT STATUS

Summarize “bottom line” in this box (to be completed by CDR Reviewer).

Manufacturer-Submitted Information Regarding Current Patent Status

The required information in this section includes:

- expiry date(s) of all Canadian patent(s) for the components