Ontario

Ministry of Health

OHIP, Pharmaceuticals and Devices Division

Ontario Guidelines for Single Source Drug Products

Submission Requirements and Review Process

Table of Contents

Introduction

The Ontario Public Drug Programs (OPDP) provides funding for a number of publicly funded drug programs. The largest program is the Ontario Drug Benefit (ODB) program and eligible benefits are listed on the ODB Formulary/Comparative Drug Index (the "Formulary"). Additional coverage may be provided through case by case review under the Exceptional Access Program (EAP).

For drug products to be considered for funding under the OPDP, a drug manufacturer must provide a complete submission in accordance with the applicable conditions set out in Ontario Regulation 201/96 made under the *Ontario Drug Benefit Act* (the "ODBA Regulation") and these Guidelines.

Objective

The objective of this document is to provide guidance on submission requirements and the ministry's review process. The Guidelines are to be used in the preparation of a drug product submission provided to the Ministry of Health (ministry). Some sections of the Guidelines are general in nature and must be read in conjunction with applicable legislation. For example, if a drug product is exempt from a submission requirement by regulation, then it will also be exempt from the corresponding section of the Guidelines. The manufacturers, or those filing submissions on their behalf, are responsible for ensuring that all drug product submissions filed with the ministry contain sufficient information to satisfy the applicable requirements of the legislation and the Guidelines.

1. Checklist for Preparing Submissions

The manufacturer may use the below checklist to help ensure that all submission requirements have been included.

Requirement:	Included
Signed cover letter	☐
Table of contents	☐
Health Canada Documentation:	
Notice of Compliance; AND	☐
Product Monograph	☐
Letter of Consent	☐
Proposed Drug Benefit Price	☐
Ability to Supply Letter	☐
Certification of Providing No Rebate Letter	☐
Clinical Evidence/Studies:	
Common Technical Document:	
Section 2.5;	☐
Section 2.7.1;	☐
Section 2.7.4; AND	☐
Section 5.	☐
OR	
†Clinical evidence, that includes:	
Comprehensive Summary or equivalent;	☐
Full efficacy and safety study report(s);	☐
Summary of critical studies;	☐
Additional studies completed after the New Drug	☐
Submission (NDS) was filed; AND	☐
Disclosure of results from all Phase II, III and IV trials	☐
List of published and unpublished studies	☐
‡Clinical Data Checklist	☐
Financial Impact Analysis:	☐
Budget Impact Analysis (BIA) (report and model); AND	☐
OPDP Financial Impact Analysis Summary Sheet	
Pharmacoeconomic Evidence:	
Pharmacoeconomic Analysis (report and model); AND	☐
Pharmacoeconomic Analysis Summary; AND	☐
‡Pharmacoeconomic Analysis Worksheet	☐

†When the Common Technical Document is not available, manufacturers may satisfy the requirement for clinical evidence by submitting the applicable information listed above.

‡The Clinical Data Checklist and Pharmacoeconomic Analysis Worksheet are waived for drug products undergoing reimbursement review by CADTH.

2. Submission Requirements for Single Source Drug Products

2.1 Cover Letter and Table of Contents

A cover letter and table of contents must accompany the submission. The cover letter must clearly state:

- The name of the drug product, the DIN of the product, its active pharmaceutical ingredient(s), strength(s), and dosage form(s) (including the various package sizes).
- The type of submission (e.g. new chemical entity, new indication, line extension, etc.).
- The type of listing requested (e.g. General Benefit, Limited Use, Exceptional Access Program, New Drug Funding Program etc.).
- Whether the manufacturer has any business agreements with any third party (e.g. consultant, cross-licensed, co-marketing, etc.) with respect to the drug product, and, if so, the name of the third party / third parties. See additional information in section 8.1 of these Guidelines.

2.2 Evidence of approval from Health Canada, including:

- A copy of the Notice of Compliance (NOC), if applicable; and
- A copy of the most recent Product Monograph approved by Health Canada, subject to the exception in section 8.2 below.

2.3 Letter of Consent

A letter from the holder of the Health Canada approval authorizing the Executive Officer to gain access to all information with respect to the Drug Product in the possession of Health Canada, the Patented Medicines Pricing Review Board, the government of any province or territory in Canada or the Canadian Agency for Drugs and Technologies in Health and authorizing the Executive Officer to disclose any information with respect to the Drug Product in the possession of the Ministry to Health Canada, the Patented Medicine Prices Review Board, the government of a province or territory in Canada or the Canadian Agency for Drugs and Technologies in Health.

See Template Letter of Consent in section 7 below.

2.4 Proposed Drug Benefit Price

Submit a proposed drug benefit price (DBP) for the Drug Product. The proposed DBP (to four decimal places) should include, where applicable:

- The price per smallest unit (e.g. tablet, capsule, gram, millilitre, etc.); and
- The price per smallest dispensable unit for each package size (e.g. bottle, kit, ampoule, pre-filled syringe, vial combination package, etc.).

2.5 Evidence Confirming Ability to Supply

Confirmation that that the manufacturer is able to supply the Drug Product at the proposed drug benefit price in a quantity sufficient to meet the anticipated demand for the Drug Product.

See Template Letter of Ability to Supply in section 7 below.

2.6 Certification Confirming That No Rebates Were Provided

The manufacturer must certify in writing that no rebates were provided to persons listed under subsection 11.5(1) of the *Ontario Drug Benefit Act* (ODBA) with respect to the Drug Product from the time that Health Canada approved the Drug Product for sale in Canada.

See Template Letter Certification of Providing No Rebate in section 7 below.

2.7 Clinical Evidence/Studies

When the Common Technical Document is available, the following information must be submitted:

- Clinical Overview – Module Section 2.5
- Summary of Biopharmaceutic Studies and Associated Analytical Methods – Module Section 2.7.1
- Summary of Clinical Efficacy – Module Section 2.7.3
- Summary of Clinical Safety – Module Section 2.7.4
- Tabular Listing of All Clinical Studies – Module Section 5.2
- Complete list of published and unpublished studies.

- Completed Clinical Data Checklist (see section 7 below)

When the Common Technical Document is not available, manufacturers may satisfy this requirement for clinical evidence/studies by submitting:

- Clinical evidence, including:
    - The Comprehensive Summary or equivalent documentation accepted by Health Canada (as described in Health Canada's New Drug Submission Guideline) and the full efficacy and safety study report(s);
    - A summary of the critical studies; any additional studies completed after the New Drug Submission (NDS) was filed;
    - Disclosure of results from all Phase II, III and IV trials and certification of full disclosure by a senior company official;
- Complete list of published and unpublished studies; and
- Completed Clinical Data Checklist.

For drug products undergoing a reimbursement review by the Canadian Agency for Drugs and Technologies in Health's (CADTH), clinical evidence / studies submitted to CADTH are acceptable, including a list of published and unpublished studies.

Submissions going through the CADTH Reimbursement Review process are exempt from providing a Clinical Data Checklist.

2.8 Financial Impact Analysis

The manufacturer should provide an estimate of the net costs to the OPDP in three-year period including:

- BIA (report and model; must include an estimate of the net costs to the OPDP in a three-year period).
- OPDP Financial Impact Analysis Summary Sheet (see section 7 below).

In assessing financial impact, the ministry is interested in yearly expenditures (drug costs only) for the product(s) under consideration. Drug costs should exclude upcharge (mark-up) and dispensing fee. The expenditures should be projected for three consecutive twelve-month periods irrespective of the anticipated date of funding. Forecasts should be provided for each individual drug product (e.g. strength and dosage form).

2.9 Pharmacoeconomic Evidence

The manufacturer must prove the benefit of its proposed product in relation to the cost of the product and to alternative products.

For drug products undergoing a reimbursement review by CADTH, the pharmacoeconomic evidence submitted to CADTH is acceptable. A completed Pharmacoeconomic Analysis Summary (see section 7 below) must also be provided.

For drug submissions that do not undergo reimbursement review by CADTH, manufacturers may satisfy this requirement for pharmacoeconomic evidence by submitting:

- A completed Pharmacoeconomic Analysis (report and model).
- A completed Pharmacoeconomic Analysis Summary (see section 7 below).
- A completed Pharmacoeconomic Analysis Worksheet (see section 7 below).

Pharmacoeconomic Analyses:

As part of the review of drug submissions, the Committee to Evaluate Drugs (CED) or Ontario Steering Committee for Cancer Drugs (OSCCD) evaluates the value-for-money of new drug product(s), particularly in comparison to alternatives already funded under OPDP. Pharmacoeconomic analyses provide the CED or OSCCD with an evidence-based opportunity to assess if there are any additional cost considerations that should be taken into account other than the cost of the medication alone.

While not all submissions to the ministry require a full cost-effectiveness analysis, some form of economic evaluation and summary is necessary for all products. A starting point would be a tabulation of costs of therapy associated with the submitted product and appropriate comparator(s) and an itemization of the important respective outcomes.

When drugs have been demonstrated to be equally effective and have similar side effect profiles, a comparison of total costs of therapy alone (i.e. a cost minimization analysis) may be appropriate. In the situation where the new product improves outcomes at a lower cost (i.e. dominant therapy), then a cost-minimization analysis is also sufficient.

If the new product has an incremental cost (drug price and/or total therapy cost) with an incremental gain in efficacy or other outcomes, then a cost-effectiveness, -utility or -benefit analysis is essential. Cost-utility analyses should be conducted when the value of the therapy seems to relate to improvements in quality-of-life.

Cost impacts outside of drug expenditures are very important in the evaluation of pharmaceutical products. These costs should be itemized carefully and realistic unit costs should be assigned from any of a number of standard resource references (e.g. case costing systems in hospitals, schedule of benefits for physicians and laboratories).

Pharmacoeconomic Analysis Worksheet:

Submissions that include a pharmacoeconomic analysis must also have a completed Pharmacoeconomic Analysis Worksheet. For each question, the manufacturer should provide a concise answer (bullet points are adequate) and direct reviewers to reference pages or tables within the body of the economic report or in the supporting literature for clarification. Submissions going through the CADTH Reimbursement Review process are exempt from providing a Pharmacoeconomic Analysis Worksheet.

Note: Unlocked (or executable) format copies of both the pharmacoeconomic model and BIA are required for all submissions. Licensed software required for data manipulation, other than Microsoft Excel, must accompany each unlocked (or executable) format copy of pharmacoeconomic model and BIA analysis.

3. Submission Requirements for Line Extension Drug Products

3.1 Submission Requirements for Additional Strengths

When manufacturers submit several strengths of a specific dosage form concurrently, or additional strengths of an already listed drug product, the above requirements in sections 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.8 and 2.9 apply.

However, the requirement for product-specific clinical studies/evidence described above in section 2.7 is modified, if the manufacturer complies with the requirements in sections 3.1.1 and 3.1.2 below. In the case of drug products seeking listing on the Ontario Drug Benefit Formulary, this modification is authorized under subsection 12(3) of the ODBA Regulation.

3.1.1 Evidence of proportionality in composition or evidence of bioequivalence

If the different drug strengths have proportional formulations or have the same ingredients with only modest changes in the quantities of inactive ingredients, a manufacturer may rely on the same clinical data for two strengths of the drug product.

Manufacturers must provide evidence that the different strengths have the same proportions (i.e. CPID/master formulation should be provided for all the strengths).

If the additional strength of the product is not proportional in composition and major formulation differences exist between the strengths, the manufacturer must submit a comparative bioavailability study demonstrating that the two strengths are bioequivalent.

3.1.2 Justification of need for the Additional Strength

Manufacturers must provide a justification for the additional strength and describe the patient population that is most likely to make use of this additional strength, including some data for the use of the additional strength of the product in the targeted patient population. The manufacturer must also estimate the proportion of patients in whom the additional strength product would be used.

3.1.3 Clinical Summary for the already listed strength of the drug product

Manufacturers must provide a summary of the clinical studies for the listed strength.

3.2 Submission Requirements for a New Format

When manufacturers submit multiple pack sizes, different dosage forms or different packaging formats of the same drug product concurrently, or a new dosage form, new packaging format or new pack size (new format) of an already-listed drug product, the above requirements in sections 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.8 and 2.9 apply.

However, the requirement for product-specific clinical studies/evidence described above in section 2.7 is modified, if the manufacturer complies with the requirements in sections 3.2.1 to 3.2.3 below. In the case of drug products seeking listing on the Ontario Drug Benefit Formulary, this modification is authorized under subsection 12(3.1) of the ODBA Regulation.

Manufacturers must clearly outline the evidence upon which Health Canada approved the new format and provide the applicable data in 3.2.1 below.

3.2.1 Evidence of Bioequivalence or Pharmaceutical Equivalence between the two formats

If there are no changes to the master formulation and the bioavailability is not affected with the new format, the manufacturer is asked to include written confirmation with the submission.

When the bioavailability of a drug product in a new format is not identical to that of the listed format of the drug product, manufacturers must submit a comparative bioavailability study demonstrating that the two formats are bioequivalent in order to rely on the clinical data for the listed format.

For different packaging formats, the manufacturers must submit evidence of pharmaceutical equivalence. Comparative stability test data demonstrating that the two formats are equivalent in terms of performance and product quality to support the entire product shelf life should be provided. In addition, a copy of the stability study protocol/design, including the testing frequency, parameters, specifications and methodologies, etc., is required.

3.2.2 Justification of need for the New Format

Manufacturers must provide a justification for the new format and describe the patient population that is most likely to make use of the new format, including data for use of the new of the product in the targeted patient population. The manufacturer must also estimate the proportion of patients in whom the new format would be used.

3.2.3 Clinical Summary for the already listed format of the drug product

Manufacturers must provide a summary of the clinical studies for the listed format.

4. Drug Submission Review Process

4.1 Filing of Drug Submissions

A manufacturer who wishes to have a drug product considered for funding under OPDP must file a submission with the ministry.

4.2 Written/Verbal Communication

All written and verbal communication between the ministry and a manufacturer takes place through a single primary contact from the manufacturer. The ministry requires written notification in order to change a manufacturer's primary contact, or any other information related to contact information (e.g. address, telephone number, e-mail address, etc.). It is the manufacturer's responsibility to keep this information current and accurate.

4.3 Submission Receipt and Review

Single source drug product submissions are screened for compliance with applicable requirements in the legislation and these Guidelines by ministry staff in sequence, according to the date and time of receipt.

For Ontario-specific submissions undergoing review by the CED or OSCCD, the targeted time frame for screening is approximately three weeks from the date the submission is received by the ministry.

Submissions undergoing reimbursement review by CADTH will be screened before the date of the expert committee meeting.

Only complete submissions (i.e. those that meet all applicable requirements) are eligible for review and consideration for funding under OPDP. Manufacturers must ensure a submission has been deemed complete before finalizing any product listing agreement for the drug product. The date that the ministry deems a submission complete, as well as the type of review (i.e. first review or reconsideration), determines the subsequent priority of the product versus another in the review process and on the CED or OSCCD agenda. The complete submission date refers to the date when the NDSS letter is sent.

4.4 Ministry Communication

Once a submission is screened by the ministry, an NDSS is issued to the manufacturer. Each submission is assigned a unique master file number, and each individual drug product within the same submission is assigned a unique drug product file number. The NDSS will indicate the status of the submission (i.e. complete or incomplete) as well as the assigned file numbers. The NDSS for an incomplete submission will state the reasons why the submission was deemed incomplete.

The ministry reserves the right to request additional information needed to address any uncertainties associated with a submission or to resolve questions that may arise during the review. The ministry, CED, or OSCCD may request additional information from manufacturers at any time during the screening and/or review process.

4.5 Manufacturer's Response

A manufacturer should make reference to the drug product (product name/generic name/strength/dosage form/package format and size), the master file number, the DIN, and the drug product file number(s) in all subsequent correspondence to the ministry. If a manufacturer receives an NDSS, which indicates that the submission was deemed incomplete, the manufacturer will be provided with 60 calendar days in which to provide the information required to complete the submission, except for pre-NOC submissions undergoing a CADTH Reimbursement Review. A pre-NOC submission received by the ministry that is undergoing a CADTH Reimbursement Review national review processes will have an alternate deadline specified on the NDSS for the manufacturer's completion of the submission.

Manufacturers are encouraged to respond to requests for additional information in a timely manner to avoid delays in the submission review process.

4.6 Review by the Advisory Committee

All drug products reviewed by the CADTH Reimbursement Review process do not require a routine review by the Committee to Evaluate Drugs (CED), the ministry's expert drug advisory committee.

This decision was made to better align with national processes, including the pan-Canadian Pharmaceutical Alliance.

On a case-by-case basis, the OPDP may seek CED or OSCCD's advice on drug products previously reviewed by the CADTH Reimbursement Review.

The CED or OSCCD will continue to review complete submissions for brand products that are not eligible for the CADTH Reimbursement Review process, as well as provide advice to the ministry on important initiatives such as formulary modernization and drug class reviews.

Non-cancer drugs are reviewed by CED, whereas cancer drugs are reviewed by OSCCD. The complete submission is sent to a reviewer who reviews the submission and prepares a written report. Submissions are reviewed by CED or OSCCD members and/or by reviewers drawn from an extensive roster of external clinical and pharmacoeconomic consultants.

The targeted time frame for the completion of the report is four to six weeks. The submission will be considered by the CED or OSCCD at the earliest available meeting.

The CED, OSCCD, or the ministry may require additional time to review complex submissions. Occasionally, a panel or subcommittee of the CED may be requested to review a specific submission, which will extend the timeline for the review.

The CED or OSCCD discusses each submission, with input from reviewers, other expert external consultants, and the ministry as required. The drug products are evaluated for the comparative therapeutic efficacy and safety for the patient populations covered by the OPDP, cost-effectiveness in comparison to currently reimbursed alternatives, patient value or input, and impact on other health services. This comprehensive evaluation contributes to the determination of value-for-money for OPDP.

4.7 Communication to Manufacturers

A recommendation letter is issued to a manufacturer after the CED or OSCCD review. The recommendation letter is sent to the manufacturer generally within four to five weeks after the ratification of the CED or OSCCD meeting minutes. The recommendation letter will summarize the CED or OSSCD's recommendation and reason(s) for its recommendation.

4.8 Time Frames

Manufacturers can track their submissions by understanding the process and tracking the correspondence they receive from the ministry. Please note that "Targeted Time-frames" indicated below are only approximate timelines and specifically for submissions applicable to CED and OSCCD reviews.

Activities	**Targeted Time-frame**
Ministry screening of submission	Three weeks (may be longer for complex submissions)
Reviewer identified for complete submission	Two to seven business days
Expert review of submission	Four to five weeks
For first review submission CED review and recommendation	Two to four months from the date a submission is deemed complete (may be longer for complex submissions)
For reconsideration review submission CED review and recommendation	As CED agenda permits

5. Format and Organization of Submissions

The OHIP, Pharmaceuticals and Devices Division accepts e-mail submissions. The submissions must be well organized and indexed/tabbed with description. Manufacturers must not provide submission information in one continuous document. If the submission is too large to be sent by a single e-mail, the ministry will accept the whole submission via multiple e-mails. If the manufacturer is sending multiple e-mails for one submission, clearly identify that the e-mails belong to the same submission and how many total e-mails pertain to that particular submission.

The ministry expects manufacturers to follow the Guidelines when preparing submissions. The onus is on a manufacturer to provide the ministry with a submission that is complete, accurate and complies with applicable legislative and policy requirements. The ministry will not assume responsibility for advising manufacturers of the completeness of their submissions prior to the ministry screening and review. Also, the ministry reserves the right to request additional information at any time during the review process.

6. Filing of Drug Submissions

All submissions and any additional related information must be sent to:
Senior Manager
Drug Benefit Management Unit
Drug Programs Policy and Strategy Branch
OHIP, Pharmaceuticals and Devices Division
Ministry of Health

Please send the submissions to email mailbox DrugSubmissions.MOH@ontario.ca

7. Templates and Checklists

Templates:

- Template Letter of Consent
- Template Letter Confirming Ability to Supply
- Template Letter Certification of Providing No Rebate

Checklists:

- Clinical Data Checklist
- OPDP Financial Impact Analysis Summary
- Pharmacoeconomic Analysis Work Sheet
- Pharmacoeconomic Analysis Summary

The ministry's template letters and checklists are available on the ministry's website. All template letters must be prepared using the appropriate manufacturer's letterhead, dated and signed by the senior company official.

8. Additional Information

8.1 Third Party Involvement

Where a third party is involved with a submission, a letter must be submitted from each of the NOC/DIN holder and the third party confirming the business arrangement between the submitting party and the NOC/DIN holder. The letter from the NOC/DIN holder must authorize the submitting party to file and discuss the submission with the ministry, on behalf of the NOC/DIN holder.

8.2 If No Product Monograph Has Been Approved

If Health Canada has not approved a Product Monograph for a drug product (e.g. "old" drugs), the manufacturer of the drug product may, instead of submitting a copy of the Product Monograph, submit the following:

- Pharmaceutical information.
- Information with respect to the product's clinical pharmacology.
- Information as to the product's indications and clinical use.
- A list of any contra-indications, warnings or precautions in the use of the product and of possible adverse reactions to its use.
- A list of symptoms of an overdose of the product and information as to the treatment of an overdose.
- Information with respect to the dosage and administration of the product.

- Information regarding the availability of dosage forms for each strength of the product marketed in Canada.

8.3 Withdrawal Process

The submitting manufacturer may voluntarily withdraw a submission any time throughout the review process. A written request must be provided by the manufacturer to the ministry with an explanation to withdraw a submission.

List of Abbreviations

BIA	Budget Impact Analysis
CADTH	Canadian Agency for Drugs and Technologies in Health
CED	Committee to Evaluate Drugs
CPID	Certified Product Information Document
DBP	Drug Benefit Price
DIN	Drug Identification Number
EAP	Exceptional Access Program
EO	Executive Officer
HC	Health Canada
NDS	New Drug Submission
NDFP	New Drug Funding Program
NDSS	Notice of Drug Submission Status
NOC	Notice of Compliance
ODB	Ontario Drug Benefit
ODBA	Ontario Drug Benefit Act
OPDP	Ontario Public Drug Programs
OSCCD	Ontario Steering Committee for Cancer Drugs
PM	Product Monograph

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