Ontario

Ministry of Health

OHIP, Pharmaceuticals and Devices Division

Ontario Guidelines for Multiple Source Drug Products

Submission Requirements and Review Process

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Introduction

Through the Ontario Public Drug Programs (OPDP), the Ministry of Health (ministry) provides funding for a number of publicly funded drug programs. The largest program is the Ontario Drug Benefit (ODB) program established under the *Ontario Drug Benefit Act* (ODBA), which funds eligible benefits (known as listed drug products and listed substances) designated the ODB Formulary/Comparative Drug Index (the "Formulary"). Additional ODB coverage may be provided for drug products through case by case review under the Exceptional Access Program (the "EAP").

The ministry is also responsible for designations of interchangeability under the *Drug Interchangeability and Dispensing Fee Act* (DIDFA).

A manufacturer submitting a multiple source drug product (i.e. a different brand of an already or previously listed drug product) for designation as a listed drug product under the ODBA and/or as an interchangebale product under the DIDFA, must provide a complete submission in accordance with the applicable conditions set out in the regulations under the ODBA and the DIDFA, 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. Checklists 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	☐
Submission Summary Sheet	☐
Health Canada Documentation: Notice of Compliance; and Product Monograph	 ☐ ☐
Letter of Consent	☐
*Certified Product Identification Document (CPID) or Master Formula	☐
Proposed Drug Benefit Price	☐
Ability to Supply Letter	☐
Certification of Providing No Rebates Letter	☐
***Comparative bioavailability studies** (or other studies) including: Completed Bioequivalence Data Checklist; Completed Pharmacokinetic/Statistical Worksheet; and Production master formulation for the biolot	☐ ☐ ☐ ☐
Letter confirming no patent infringement	☐
Business agreement letters from both parties	☐
Product Confirmation Letters from both parties	☐

*Streamlined multiple source submissions are exempt from providing the CPID or Master Formula, comparative bioavailability studies, Bioequivalence Data Checklist, Pharmacokinetic/Statistical Worksheet, and production master formula for the biolot.

2. Streamlined vs. Non-Streamlined

The review process for multiple source product submissions differs depending on whether the submission is classified as (1) streamlined, or (2) non-streamlined.

A streamlined submission is one that does not undergo review by the Committee to Evaluate Drugs (CED). A submission is streamlined if it relates to a multiple source (i.e. generic) product that has received a declaration of equivalence (DOE) from Health Canada with the brand reference product or another listed interchangeable product with which the generic product would be designated as interchangeable.

A submission is also streamlined if it relates to a pseudogeneric product – i.e. a generic product with the same dosage form, strength, formula, manufacturing process, raw material testing standards, as the product with which it seeks to be designated as interchangeable. Generic product cross-referenced to another listed generic product does not qualify as a pseudogeneric drug product.

Streamlined multiple source submissions are exempt from providing the CPID or Master Formula, comparative bioavailability studies, Bioequivalence Data Checklist, Pharmacokinetic/Statistical Worksheet, and production master formula for the biolot.

Non-streamlined submissions are reviewed by the CED. A submission is non-streamlined if it relates to a generic product without a DOE with the brand reference product or another listed interchangeable product with which the generic product would be designated as interchangeable.

3. Information Requirements for Streamlined Drug Submissions

If a manufacturer submits a streamlined submission the following information must be provided:

3.1 Cover Letter

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 generic drug product, additional strength, additional dosage form, generic line extension, multiple source for single source listing, re-designation of a previously designated multiple source product etc.).

The type of listing requested:

- Designation as a listed drug product and an interchangeable product (e.g. General Benefit, Limited Use).
- Funding under EAP and designation as an interchangeable product.
- Designation as a listed drug product only (e.g. multiple source product for single source listing, such as General Benefit or Limited Use).
- Designation as an interchangeable product only (e.g. Off-Formulary Interchangeability (OFI)).
- Funding under OPDP as a generic, other than the ODB Program (e.g. New Drug Funding Program (NDFP).

- Whether the manufacturer has any business agreements with any third party (e.g. consultant, cross-licensed, co-marketing, etc.) with respect to the multiple source product, and, if so, the name of the third party / third parties. See additional information in section 14.1 of these Guidelines.

3.2 Submission Summary Sheet

Every submission must include a copy of the completed Submission Summary Sheet.

3.3 Evidence of approval from Health Canada, including:

- A copy of the Notice of Compliance (NOC), if applicable. The manufacturer must confirm the Drug Identification Number (DIN) for the product if it does not appear on the supplemental NOC, i.e. provide the original NOC.
- A copy of the most recent Product Monograph approved by Health Canada, subject to the exception in section 14.2 below.

Note: If the Product Monograph has been updated, the manufacturer is required to provide evidence of Health Canada's approval (e.g. NOC or No Objection Letter) and the most updated Product Monograph (annotated/ tracked and non-annotated) with the most recent date of revision and control number.

3.4 Letter of Consent

A letter from the holder of the Health Canada approval for the multiple source drug product 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 13 below.

3.5 Proposed Drug Benefit Price

Submit a proposed drug benefit price (DBP) for the multiple source 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.).

If the price of the smallest unit is accepted by the ministry and listed on the Formulary, it will apply to all package sizes of the product.

3.6 Evidence Confirming Ability to Supply

Confirmation that the manufacturer is able to supply the multiple source drug product at the proposed drug benefit price in a quantity sufficient to meet the anticipated demand for the drug product. The ability to supply letter is not required for OFI submissions.

See Template Letter of Ability to Supply in section 13 below.

3.7 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 13 below.

3.8 Letter Confirming No Patent Infringement

In order to mitigate the risk of regulatory non-compliance or inducing patent infringement, the ministry has initiated a policy to require manufacturers to advise the ministry that there is no outstanding patent issue for the multiple source product in the submission. The ministry is not looking to enforce patent matters but rather to be made aware of any potential patent infringement prior to any potential designation on the Formulary. The purpose of this requirement is for drug manufacturers to inform the Executive Officer of any limitations on their ability to market or sell the product. The ministry has, in the past, limited or qualified the designation of a multiple source product due to patent-related restrictions on its use.

See Template Letter of Patent Status in section 13 below.

4. Information Requirements for Non-Streamlined Drug Submissions

When manufacturers submit a non-streamlined submission, the above requirements in sections **3.1 to 3.8** apply. In addition, the following information relating to interchangeability must be provided:

4.1 Evidence of interchangeability

4.1.1 Comparative bioavailability studies on humans, comparative clinical studies on humans, or both, or other in vivo studies that will show the interchangeability of the product with the original product (full reports of comparative bioavailablility studies);

4.1.2 Completed Bioequivalence Data Checklist; and

4.1.3 Completed Pharmacokinetic/Statistical Worksheet.

Note: The Bioequivalence Data Checklist and the Pharmacokinetic/Statistical Worksheet were developed based on the guidelines that the CED uses during its evaluation. They were designed to help manufacturers prepare submissions that are easy to review and ensure submissions proactively address the CED's anticipated questions. For each question on the Bioequivalence Data Checklist, manufacturers should provide short answers below the question and direct the CED to the supporting reference page(s).

Please indicate not applicable (N/A) on the checklist and provide a rationale, if necessary, if a question on the Bioequivalence Data Checklist does not apply.

4.1.4 Completed production master formulation for the biolot

The submission must include the production master formulation for each of the multiple source products used in the studies. The production master formulation refers to the production manufacturing documentation for the test lot (biolot). The document must provide the list of ingredients used to manufacture the drug product of lot/batch number indicated in the bioequivalence study. In addition, the manufacturer must convert the batch record information into the smallest quantity per unit sample of the drug product, dated and signed by the senior quality assurance personnel.

4.2 Documentation disclosing the product's master formulation

The Completed Certified Product Information Document (CPID) that was approved by Health Canada or production master formulation (calculated per smallest unit) must be provided.

Note: If the manufacturer does not have a CPID approved by Health Canada, the ministry may accept a copy of the master formulation for the drug product originally approved by Health Canada. The approved master formulation must contain the product name as described in the NOC, dated and signed by the appropriate quality control personnel.

The master formulation must provide:

- The list of ingredients used to formulate the drug product;
- The information about the bulk formulation (granulation or liquid), if applicable;
- The information about coating ingredients, if applicable; and
- The information about the finished product expressed in the smallest quantity per unit (e.g. mg/tablet, mg/mL, etc.).

When the master manufacturing batch record is provided as evidence of product formulation, the manufacturer must convert the list of ingredients in the batch record into the smallest quantity per unit required in manufacturing a drug product.

Note: If the formulations are not proportional, the comparative bioavailability studies for the other strengths will be required.

5. Special Cases

When a comparative bioavailability study cannot be conducted the ministry may consider other studies comparing the safety and efficacy of the multiple source product and the original product.

5.1 Evaluation of Studies

In the case of pharmacodynamic studies, assessment is individualized and appropriate to the class of drugs under consideration. Manufacturers must ensure that pharmacodynamic studies are able, through both study design and sample size, to detect clinically important differences.

The CED evaluates both the experimental and statistical evidence. This examination may include the power of the study, the array of raw data, sample summary statistics and kinetic plots for individual subjects. Further analyses normally consist of statistical tests such as:

- t-test or ANOVA;
- comparison of observed differences observed between means of appropriate end point parameter(s) with 90% Confidence Intervals constructed about these means to convey the degree of variability in the difference.

Notwithstanding the above, the ministry may allow the acceptability criteria to be more or less stringent, depending on the clinical evidence.

5.2 Aqueous solutions and non-aqueous oral solutions

Manufacturers seeking an interchangeability designation for aqueous solutions and non-aqueous oral solutions (i.e. alcohol co-solvent solutions) may provide physicochemical data between the submitted drug and the listed original/innovator product in lieu of *in vivo* bioequivalence data for the evaluation of interchangeability.

Manufacturers should provide comparative physicochemical data as described below to demonstrate the product's pharmaceutical equivalence with the original/innovator product.

<u>Physicochemical Evaluation Criteria and Testing Specifications:</u>

In submitting information on test parameters, where summary tables of results are submitted, supporting documentation must be enclosed (i.e. Certificates of Analysis/ worksheets of the submitted product, or worksheets for the reference product).

Manufacturers must provide information on all of the required parameters as specified under each type of solution. Where test results are not provided for a given parameter, the manufacturer must include a justification for the missing parameter.

Tests must be completed on packaged, unopened product (i.e. finished product) and testing should be from the same lot. Preferably, the tests should be conducted for a current lot of the drug product. The lot numbers and the expiry dates of the submitted and reference products must be provided. The test lot must be of the formulation marketed in Canada. Test results from a different lot may be accepted if the manufacturer provides evidence that the formulations are similar (i.e. the formulations of all lots should be submitted).

The ministry will not accept a signed summary table of the list of ingredients used to manufacture a drug product as the official document for CPID or master formulation. Refer to section 4.2 above for details on CPID.

The test documentation must include the information on the description of test, test specification and preferably method reference. The testing documentation must be dated and signed by a senior company official.

Test results from a lot up to one year post-expiry (as of the date of submission) may be accepted if the manufacturer provides evidence that the formulations are similar (i.e. the formulations of all lots should be submitted).

The Drug Submission Checklist for Aqueous Solutions and Non-Aqueous Oral Solutions must be provided. See Section 13 below.

Note: This exemption does not apply to suspensions, emulsions, or oil-based injections or solutions and dermatological products.

5.3 Metered dose inhalers and Special Delivery Devices

When the manufacturer is seeking an interchangeability designation for drug products such as metered dose inhalers, ophthalmic suspensions or special delivery devices such as autoinjector pens and prefilled syringes, where pharmaceutical equivalence cannot be used as a surrogate for bioequivalence, the ministry may consider comparative pharmacodynamic/clinical studies of the product requested for designation and the original product, which compare efficacy and safety. In rare instances, a pharmacokinetic assessment in an appropriate animal study may provide evidence of interchangeability.

With pharmacodynamic and/or pharmacokinetic studies, the ministry requires the following documentation:

- A detailed protocol, including a description of inclusion and exclusion criteria, subject numbers, demographics, and a discussion of the statistical analyses applied, including the statistical power of the study design;
- Evidence the protocol was approved for safety and ethics by a qualified, independent review committee; and
- All resulting data and appropriate analyses in a form suitable for scientific review including Confidence Intervals or some measure of variability constructed about endpoints to allow interpretation of the differences.

5.4 Non-aqueous ophthalmic, otic and nasal preparations

When the manufacturer is seeking an interchangeability designation for non-aqueous ophthalmic preparation, both comparative in-vitro and bioavailability/clinical data are required. Manufacturers submitting non-aqueous ophthalmic, otic and nasal preparations must provide comparative data for:

- Droplet size;
- The amount of drug delivered per drop (the delivery systems must dispense consistent and comparable amounts); and
- Distribution coefficient.

5.5 Suspensions, emulsions or oil-based solutions

When the manufacturer is seeking an interchangeability designation for a suspension, emulsions or oil-based solutions, a properly designed bioavailability or bioequivalence study (i.e. pharmacodynamic) must be carried out using Health Canada's Bioavailability and Bioequivalence Guidance Documents with the endpoint evaluation ideally being at 90% or 95% CI falling completely within 80-125% bounds.

Where this is not possible, a pharmacodynamic study with appropriate endpoints should be completed and the endpoints justified. See Section 5.1.

5.6 Non-Systemic effect drug products

When manufacturers submit a drug product for non-sytemic effect, where blood concentrations of the product cannot be measured and clinical studies with a pharmacodynamic endpoint are inappropriate to conduct, the manufacturer must submit in-vitro studies that are scientifically justified, appropriate for the drug class and can demonstrate equal drug product performance.

The scientifically justified in-vitro studies must satisfy the Executive Officer that the product is interchangeable with the original product.

Additional test studies may be required as necessary to designate interchangeability, include providing a clinical trial with a pharmacodynamics endpoint.

Guidance on the in-vitro test for oral products for local effect in the gastrointestinal (G.I) tract:

- Scientific justification for the proposed in-vitro studies;
- Evidence that the product formulations are qualitatively and quantitatively the same between the submitted products and the reference products;
- Standard comparative dissolution profiles between the test and reference products are completed in 3 different media, each of a different pH, ranging between a pH of 1 and 7. Dissolution profile test results must meet f2 condition as per dissolution test standard. That is, at least 12 units should be used for each profile determination. The % coefficient of variation of the assay of the active ingredient at the earlier time point should not be more than 20% and at other time points should not be more than 10% (refer to Health Canada's standard for dissolution profile test); and
- Evidence of formulation proportionality is required when multiple strengths of drug products are submitted i.e. CPID or master formulation for all strengths.

For other drug classes, the manufacturers are strongly encouraged to submit their proposed studies for the drug class for review prior to making a formal submission to the ministry for review.

6. Information Requirements for Multiple Source for Single Source Listing Products

Manufacturers may request the designation of a generic product as a single source product under subsection 12(4) of O. Reg. 201/96 made under ODBA, if another brand/dosage form/strength of the particular drug is not already designated as a listed drug product on the Formulary. A submission that relies on subsection 12(4) of O. Reg, 201/96 under the ODBA requires review by the CED.

When a manufacturer requests the designation of a a generic product as a single source product under subsection 12(4) of O. Reg. 201/96 under the the ODBA, the requirements in the Ontario Guidelines for Single Source Drug Products apply.

In addition, the following requirements must be provided:

- A completed Clinical Data Checklist;
- Published pivotal clinical trials for the reference product; and
- Evidence of bioequivalence with the reference product.

Note: Manufacturers must demonstrate that the submitted product is bioequivalent to the reference product. This requirement can be satisfied by providing a comparative bioavailability study, completed copies of the Bioequivalence Data Checklist, Pharmacokinetic/Statistical Worksheet, and the master formulation of the biolot.

7. Information Requirements for Generic Line Extension Products

A “generic line extension drug product” means a drug product with the same active ingredient or ingredients in the same or similar dosage form as an original product, but in a strength for which no original product exists.

A manufacturer can request the designation of a generic line extension product as a listed drug product under the ODBA. This type of submission requires review by the CED.

For a generic line extension product submission, manufacturers are required to comply with the requirements in the Ontario Guidelines for Single Source Drug Products .

In addition, the following requirements must be provided:

- The scientific evidence upon which Health Canada approved the generic line extension drug product for sale in Canada.
- The Certified Product Identification Document (CPID) or Master Formula as evidence of formulation proportionality for the submitted strength(s).
- Justification for the therapeutic need for the new strength.
- An estimate of the net costs to the ODB Program in three-year period including:
    - Budget Impact Analysis (report and model; must include an estimate of the net costs to the ODB Program in a three-year period); and
    - OPDP Financial Impact Analysis Summary Sheet.

8. Information Requirements for Natural Health Products

The ministry funds a limited number of products that are currently designated as listed drug products on the Formulary but have been transitioned and classified by Health Canada as “Natural Health Products” (NHPs). NHPs are used and marketed for a number of health reasons, like the prevention or treatment of an illness or condition, the reduction of health risks, or the maintenance of good health.

NHPs may include vitamins, minerals and other products like amino acids and essential fatty acids. It is intended that these products will continue to be funded under the ODB program, provided that they continue to satisfy the requirements for designation as listed drug products on the Formulary set out in O. Reg. 201/96 under the ODBA.

The ministry will consider funding a new generic NHP if it is seeking interchangeability with an existing NHP currently designated as a listed drug product on the Formulary.

Since the manufacturer may not have received a Notice of Compliance (NOC) for its proposed NHP, the manufacturer must submit evidence of valid market authorization to sell the NHP in Canada to demonstrate that the product has been approved by Health Canada by providing:

- A copy of the completed, dated and signed Product Licence Application Form (PLA-Form) approved by Health Canada;
- A copy of the Product Licence with Product Number issued by Health Canada;
- A copy of the Site Licence; and

- A copy of the Product Monograph (refer to section 14.2 below for more details).

Subject to the above, the submission requirements for a generic NHP are the same as the requirements for a non-streamlined multiple source drug product (see Section 4 of these Guidelines).

9. Information Requirements for Over the Counter (OTC) Products

Many provisions in the DIDFA do not apply to OTC products. As a result, the ministry will only consider interchangeability requests for generic products that have the same strengths, dosage form and formats as existing OTC drug products designated as listed drug products on the Formulary. Section 3 and, if applicable, section 4 of these Guidelines apply to an OTC product eligible for submission.

The ministry does not consider submissions for interchangeability, if the reference product is an OTC product which is currently listed as 'not-a-benefit' or has been de-designated as a listed drug product from the Formulary. The ministry also does not consider submissions for OTC products for Off-Formulary interchangeability designation.

10. Drug Submission Review Process

10.1 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.

10.2 Written/Verbal Communication

All written and verbal communication between the ministry and a manufacturer must take 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.

10.3 Submission Receipt and Review

Multiple 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.

In order for a multiple source drug product (ODB listed drug product and OFI) to be considered for inclusion in a future monthly Formulary update by the Executive Officer, the submission must be received by the new submission deadline (date and time). The new submission deadline dates for generic drug products are available on the ministry's website. There are no exceptions for late submissions.

Only complete submissions, i.e. those that meet all applicable requirements, are eligible for review and consideration for interchangeabilty and / or funding under OPDP.

If a submission is incomplete, the manufacturer's provision of additional information to complete the submission is subject to the subsequent monthly submission deadlines for the corresponding monthly Formulary updates. The complete submission date refers to the date when the NDSS letter is sent out.

The ministry endeavours to process streamlined multiple source submissions (for designation as listed drug products under the ODBA) one week after the monthly new submission deadline cut-off date, and for OFI submissions, two weeks after the new submission deadline cut-off date.

When the manufacturers plan to make multiple submissions to the ministry within one submission cycle, please contact the ministry ahead of time to notify the ministry of the large upcoming submission volume. If a manufacturer plans to submit more than 6 molecules for Formulary listing within one submission cycle, the manufacturer is strongly encouraged to notify the ministry at least 1-2 months in advance, so that the ministry can plan and allocate resources accordingly.

10.4 Ministry Communication

Once a submission is screened by the ministry, a 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 and CED may request additional information from manufacturers at any time during the screening and/or review process.

10.5 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 a 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. If the submission remains incomplete, after 60 days from the date manufacturers receive a NDSS letter, it will be withdrawn without prejudice to refiling.

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

10.6 Review by the Advisory Committee

Complete submissions evaluated through the non-streamlined process undergo review by the ministry's expert advisory committee, the CED. The complete submission is sent to a committee member who reviews the submission and prepares a written report. Submissions are reviewed by committee members and/or by other reviewers retained by the ministry who are drawn from an extensive roster of external clinical and pharmacoeconomic consultants. The targeted time frame for the completion of reviews is four to six weeks. The CED or the ministry may require additional time to review complex submissions. Occasionally, a panel or subcommittee of the larger committee may be requested to review a specific submission, which will extend the timeline for the review.

10.7 Communication to Manufacturers

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

10.8 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.

Streamlined Generic Submissions

Activities	Targeted Time-frame
Ministry screening of submission	Submissions received by 3:00 p.m. on the new submission deadline date are screened in one week (ODB-Benefit products) or two weeks (OFI products)
Ministry notification of submission status and recommendation, if applicable	NDSS letters are sent out two weeks (ODB-Benefit products) or three weeks (OFI products) after the published new submission deadline for complete or incomplete submissions. Response required within one to two business day(s) if drug data (e.g. DIN/submitted price) are incorrect. Otherwise, no response is required for complete submissions. Incomplete submissions will not be considered for listing until additional information is reviewed, and the submissions are deemed complete.
Notice of final acceptance (OPDD Notice) – for positive listing decisions	Approximately one week prior to the effective Formulary/CDI listing date, and approximately 7 weeks after the NDSS letter is issued (dependant on EO approval).

Non-streamlined Generic Submissions

Activities	Targeted Time-frame
Ministry screening of submission	Submissions received by 3:00 p.m. on the new submission deadline date are screened in one week (ODB-Benefit products) or two weeks (OFI products)
Ministry notification of submission status and recommendation, if applicable	NDSS letters are sent out two weeks (ODB-Benefit products) or three weeks (OFI products) after the published new submission deadline for complete or incomplete submissions. Response required within one to two business day(s) if drug data (e.g. DIN/submitted price) are incorrect. Otherwise, no response is required for complete submissions. Incomplete submissions will not be considered for listing until additional information is reviewed, and the submissions are deemed complete.
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
Notice of final acceptance (OPDD Notice) – for positive listing decisions	Approximately one week prior to the effective Formulary/CDI listing date

11. 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.

12. 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

13. Templates and Checklists

Templates:

- Template Letter of Consent
- Template Letter Confirming Ability to Supply
- Template Letter Certification of Providing No Rebate
- Template Letter Current Patent Status
- Template Letter of Product Confirmation

Checklists:

- Submission Summary Sheet
- Bioequivalence Data Checklist
- Pharmacokinetic/Statistical Work Sheet
- Clinical Data Checklist
- OPDP Financial Impact Analysis Summary
- Drug Submission Checklist for Aqueous Solutions and Non-Aqueous Oral Solutions

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.

14. Additional Information

14.1 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.

In addition, the following must be provided:

- Product Confirmation Letters from both parties must be provided.

See Template Letter of Product Confirmation in section 13 above.

- The Consent Letters. All parties which may have information on file with Health Canada, other provinces and other affiliated groups relating to the product must provide a consent letter allowing communication with these in accordance with section 6(1) (b) of the DIDFA Regulation.

If the submission makes reference to another company's drug product, then the consent letter should be provided by both companies, one making the submission as well as the company of the drug product which is referred to.

See Template Letter of Consent in section 13 above.

- Notice of Compliance (NOC). The NOC from both the NOC holder and the third party (cross-licensed/referenced etc.) who has information filed with Health Canada is required. The original NOC from the cross-referenced product must be submitted.

14.2 If No Product Monograph Has Been Approved

If Health Canada has not approved a Product Monograph for a drug product (e.g. "old" drugs, new NHPs eligible to make OPDP submissions, etc.), the manufacturer of the drug product should, 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.

14.3 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.

14.4 Non-Canadian Reference Product (NCRP)

A "Canadian Reference Product" (CRP) means a drug in respect of which Health Canada has issued a NOC pursuant to section C.08.004 of the federal Food and Drug Regulations and which is marketed in Canada by the innovator of the drug.

The ministry will only accept a NCRP as equivalent to the CRP if that NCRP conforms to Health Canada's criteria and has been approved by Health Canada.

In addition, the CRP must be recognized by the ministry as the original/innovator product. The manufacturer must indicate in the cover letter if a NCRP is used in the submission.

14.5 Challenge of Interchangeability Process

A "challenge" refers to information submitted to the ministry disputing a competitor's submission or product designation (e.g. interchangeability designation, efficacy and safety issue with proposed interchangeability, etc.).

The ministry will not consider challenges for streamlined submissions. Challenges to this designation should be referred to Health Canada as the issuer of the DOE between the multiple source product and the reference brand product.

The ministry will only accept a challenge for a non-streamlined submission. The CED will consider only one challenge for a given product based on first challenge received by the ministry.

14.6 Generic-to-Generic Comparisons for the Designation of Interchangeability

The ministry will accept another generic product as the reference product, provided the generic reference product used has been designated as interchangeable with the original/innovator product. The original/innovator product will continue to be considered as the reference product for the interchangeability category.

14.7 Original Product No Longer Listed and Discontinued Drug Products

The ministry will accept submissions to designate a multiple source product as a listed drug product and as interchangeable with an original/innovator product that was, but is no longer, designated on the Formulary as a listed drug product (e.g. products that have been discontinued or delisted at the request of the manufacturer).

14.8 Submitted Product vs. Drug Product used in Bioequivalence Study

In cases where the drug product used in the bioequivalence study is different from the submitted product (e.g. different product name, different manufacturing source or manufacturer name, etc.), evidence is required to demonstrate the linkage between the product used in the study and the product submitted for listing.

A copy of the production master formulation of the test lot and a letter confirming that the two formulations and manufacturing processes are identical, except for markings and labeling are required. The letter should be dated and signed by a senior company official. Should questions arise, it may be necessary to provide further information including the documentation regarding the manufacturing and quality control (e.g. production worksheets, Certificates of Analysis of active raw material/ finished products).

14.9 Similar / Comparable Dosage Forms Eligible for Interchangeability Evaluation

The Executive Officer may designate a product as being interchangeable with another product if it is in the public interest to do so and if the product contains a drug or drugs in the same amounts of the same or similar active ingredients in the same or similar dosage form as the other product. Similar active ingredients are defined to mean different salts, esters, complexes or solvates of the same therapeutic moiety. Different isomers will not be considered for interchangeability.

List of Abbreviations

BIA	Budget Impact Analysis
CPID	Certified Product Information Document
DBP	Drug Benefit Price
DIN	Drug Identification Number
DIDFA	Drug Interchangeability and Dispensing Fee Act
DOE	Declaration of Equivalence
EAP	Exceptional Access Program
EO	Executive Officer
HC	Health Canada
NCRP	Non-Canadian Reference Product
NDFP	New Drug Funding Program
NDSS	Notice of Drug Submission Status
NHP	Natural Health Product
NOC	Notice of Compliance
ODB	Ontario Drug Benefit
ODBA	Ontario Drug Benefit Act
OFI	Off-Formulary Interchangeable
OPDP	Ontario Public Drug Programs
OTC	Over the Counter
PM	Product Monograph

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